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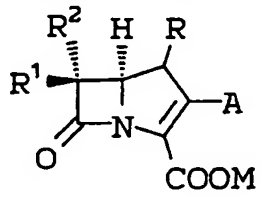
(54) 2-phenanthridonyl carbapenems.

(57) Carbapenems of the formula



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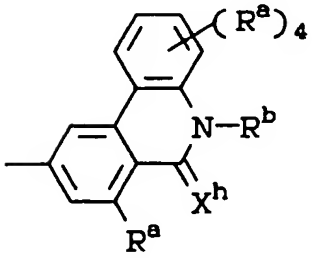

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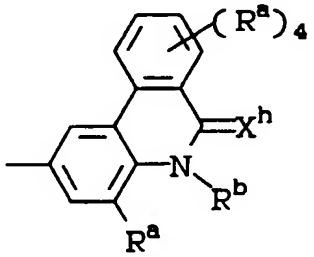


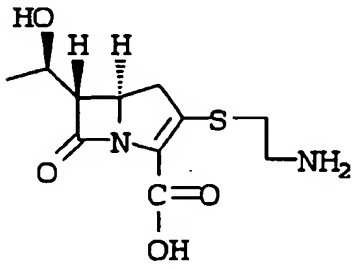
are useful antibacterial agents.

EP 0 509 780 A1

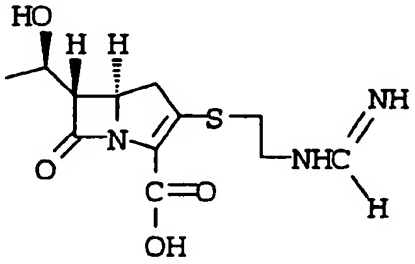
BACKGROUND OF THE INVENTION

The present invention relates to antibacterial agents of the carbapenem class, in which the 2-position side-chain is characterized by a phenanthridonyl moiety, substituted by various neutral substituents, as described in more detail further below.

Thienamycin was an early carbapenem antibacterial agent having a broad spectrum; it has the following formula:

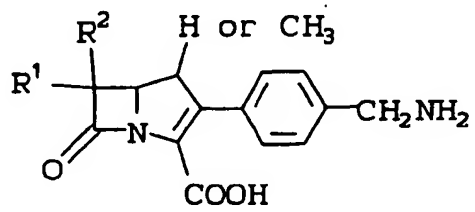


Later, N-formimidoyl thienamycin was discovered; it has the formula:



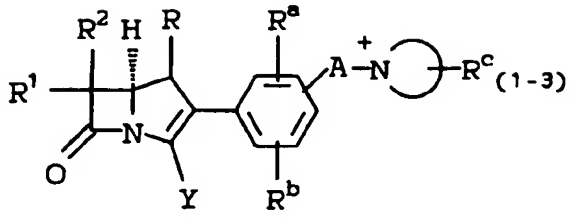
The 2-phenanthridonyl-carbapenems of the present invention are not characterized by a broad antibacterial spectrum such as that of thienamycin or N-formimidoyl thienamycin. Rather, their spectrum of activity is largely limited to gram positive microorganisms, especially methicillin resistant Staphylococcus aureus (MRSA), methicillin resistant Staphylococcus epidermidis (MRSE), and methicillin resistant coagulase negative Staphylococci (MRCNS). The antibacterial compounds of the present invention thus comprise an important contribution to therapy of these difficult to control pathogens. Moreover, there is an increasing need for agents effective against such pathogens (MRSA/MRCNS) which are at the same time safe, i.e., free from undesirable toxic side effects. No β-lactam antibacterial has yet been found which meets these requirements. And, the current agent of choice, vancomycin, a glycopeptide antibacterial, is experiencing an ever increasing amount of resistance in the MRSA/MRCNS pathogens.

More recently, carbapenem antibacterial agents have been described which have a 2-substituent which is an aryl moiety optionally substituted by, e.g., aminomethyl and substituted aminomethyl. These agents are described in U.S. Patent Nos. 4,543,257 and 4,260,627 and have the formula:



However, there is no description or suggestion of a phenanthridonyl 2-substituent such as characterizes the compounds of the present invention, nor is there any suggestion of the suprisingly better anti-MRSA/MRCNS activity of the compounds of the present invention.

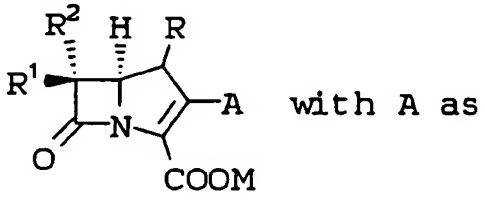
US-4,978,659 describes a particular class of compounds of the formula:



but this limited teaching in no way suggests the totally different compounds of the present invention, nor their surprisingly better anti-MRSA/MRCNS activity.

SUMMARY OF INVENTION

The present invention provides novel carbapenem compounds of the formula:



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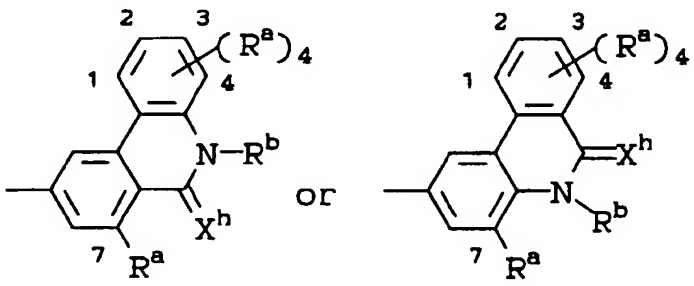


wherein:

R is H or CH_3;

R^1 and R^2 are independently H, CH_3-, CH_3CH_2-, $(CH_3)_2CH$-, $HOCH_2$-, $CH_3CH(OH)$-, $(CH_3)_2C(OH)$-, $FCH_2CH(OH)$-, $F_2CHCH(OH)$-, $F_3CCH(OH)$-, $CH_3CH(F)$-, CH_3CF_2-, or $(CH_3)_2C(F)$-;

X^h is O or S;

R^a are independently selected from the group consisting of hydrogen and the radicals set out below, provided that not more than four R^a and R^b radicals are other than hydrogen:

a) a trifluoromethyl group: $-CF_3$;

b) a halogen atom: -Br, -Cl, -F, or -I;

c) C_1-C_4 alkoxy radical: $-OC_{1-4}$ alkyl, wherein the alkyl is optionally mono-substituted by R^q, where

R^q is a member selected from the group consisting of -OH, $-OCH_3$, -CN, $-C(O)NH_2$, $-OC(O)NH_2$, CHO, $-OC(O)N(CH_3)_2$, $-SO_2NH_2$, $-SO_2N(CH_3)_2$, $-SOCH_3$, $-SO_2CH_3$, -F, $-CF_3$, $-COOM^a$ (where M^a is hydrogen, alkali metal, methyl or phenyl), tetrazolyl (where the point of attachment is the carbon atom of the tetrazole ring and one of the nitrogen atoms is mono-substituted by M^a as defined above) and $-SO_3M^b$ (where M^b is hydrogen or an alkali metal);

d) a hydroxy group: -OH;

e) a carbonyloxy radical:

$-O(C=O)R^s$, where

R^s is C_{1-4} alkyl or phenyl, each of which is optionally mono-substituted by R^q as defined above;

f) a carbamoyloxy radical:
$-O(C=O)N(R^y)R^z$ where

R^y and R^z are independently H, C_{1-4} alkyl (optionally mono-substituted by R^q as defined above), together a 3- to 5-membered alkylidene radical to form a ring (optionally substituted with Rq as defined above) or together a 2- to 4-membered alkylidene radical, interrupted by -O-, -S-, -S(O)- or $-S(O)_2-$ to form a ring (where the ring is optionally mono-substituted with Rq as defined above);

g) a sulfur radical: $-S(O)_n-R^s$ where n = 0-2, and R^s is defined above;

h) a sulfamoyl group: $-SO_2N(R^y)R^z$ where R^y and R^z are as defined above;

i) azido: N_3

j) a formamido group: $-N(R^t)(C=O)H$,
where

R^t is is H or C_{1-4} alkyl, and the alkyl thereof is optionally mono-substituted by R^q as defined above;

k) a (C_1-C_4 alkyl)carbonylamino radical: $-N(R^t)(C=O)C_{1-4}$ alkyl, where R^t is as defined above, and the alkyl group is also optionally mono-substituted by Rq as defined above;

l) a (C_1-C_4 alkoxy) carbonylamino radical: $-N(R^t)(C=O)OC_{1-4}$ alkyl, where R^t is as defined above, and the alkyl group is also optionally mono-substituted by R^q as defined above;

m) a ureido group: $-N(R^t)(C=O)N(R^y)R^z$ where R^t, R^y and R^z are as defined above;

n) a sulfonamido group: $-N(R^t)SO_2R^s$, where R^s and R^t are as defined above;

o) a cyano group: -CN;

p) a formyl or acetalized formyl radical: $-(C=O)H$ or $-CH(OCH_3)_2$;

q) (C_1-C_4 alkyl)carbonyl radical wherein the carbonyl is acetalized: $-C(OCH_3)_2C_{1-4}$ alkyl, where the alkyl is optionally mono-substituted by Rq as defined above;

r) carbonyl radical: $-(C=O)R^s$, where R^s is as defined above;

s) a hydroximinomethyl radical in which the oxygen or carbon atom is optionally substituted by a C_1-C_4 alkyl group: $-(C=NOR^z)R^y$ where R^y and R^z are as defined above, except they may not be joined together to form a ring;

t) a (C_1-C_4 alkoxy)carbonyl radical: $-(C=O)OC_{1-4}$ alkyl, where the alkyl is optionally mono-substituted by Rq as defined above;

u) a carbamoyl radical: $-(C=O)N(R^y)R^z$ where R^y and R^z are as defined above;

v) an N-hydroxycarbamoyl or N(C_1-C_4 alkoxy)carbamoyl radical in which the nitrogen atom may be additionally substituted by a C_1-C_4 alkyl group: $-(C=O)-N(OR^y)R^z$ where R^y and R^z are as defined above, except they may not be joined together to form a ring;

w) a thiocarbamoyl group: $-(C=S)N(R^y)(R^z)$ where R^y and R^z are as defined above;

x) carboxyl: $-COOM^b$, where M^b is as defined above;

y) thiocyanate: -SCN;

z) trifluoromethylthio: $-SCF_3$;

aa) tetrazolyl, where the point of attachment is the carbon atom of the tetrazole ring and one of the nitrogen atoms is mono-substituted by hydrogen, an alkali metal or a C_1-C_4 alkyl optionally substituted by R^q as defined above;

ab) an anionic function selected from the group consisting of:
phosphono [$P=O(OM^b)_2$]; alkylphosphono {$P=O(OM^b)$-[$O(C_1$-C_4 alkyl)]}; alkylphosphinyl [$P=O(OM^b)$-(C_1-C_4alkyl)]; phosphoramido [$P=O(OM^b)N(R^y)R^z$ and $P=O(OM^b)NHR^x$]; sulfino (SO_2M^b); sulfo (SO_3M^b); acylsulfonamides selected from the structures $CONM^bSO_2R^x$, $CONM^bSO_2N(R^y)R^z$, $SO_2NM^bCON(R^y)R^z$; and SO_2NM^bCN, where

R^x is phenyl or heteroaryl, where heteroaryl is a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, in which a carbon atom is the point of attachment, in which one of the carbon atoms has been replaced by a nitrogen atom, in which one additional carbon atom is optionally replaced by a heteroatom selected from O or S, and in which from 1 to 2 additional carbon atoms are optionally replaced by a nitrogen heteroatom, and where the phenyl and heteroaryl are optionally mono-substituted by R^q, as defined above; M^b is as defined above; and R^y and R^z are as defined above;

ac) C_5-C_7 cycloalkyl group in which one of the carbon atoms in the ring is replaced by a heteroatom selected from O, S, NH or N(C_1-C_4 alkyl) and in which one additional carbon atom may be replaced by NH or N(C_1-C_4 alkyl), and in which at least one carbon atom adjacent to each nitrogen heteroatom has both of its attached hydrogen atoms replaced by one oxygen thus forming a carbonyl moiety and there are one or two carbonyl moieties present in the ring;

ad) C_2-C_4 alkenyl radical, optionally monosubstituted by one of the substituents a) to ac) above and phenyl which is optionally substituted by Rq as defined above;

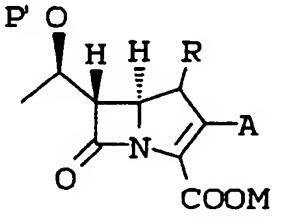
ae) C_2-C_4 alkynyl radical, optionally monosubstituted by one of the substituents a) to ac) above;
af) C_1-C_4 alkyl radical;
ag) C_1-C_4 alkyl mono-substituted by one of the substituents a) - ac) above;
ah) a 2-oxazolidinonyl moiety in which the point of attachment is the nitrogen atom of the oxazolidinone ring, the ring oxygen atom is optionally replaced by a heteroatom selected from -S- and NR^t (where R^t is as defined above) and one of the saturated carbon atoms of the oxazolidinone ring is optionally mono-substituted by one of the substituents a) to ag) above;

R^b is -H, -OH, $-CF_3$, $-(C=O)R^s$, $-S(O)_nR^s$ where n = 0-2, $-SO_2NR^yR^z$, $-(C=O)OC_{1-4}$alkyl, $-(C=O)N(R^y)R^z$, $-(C=O)N(OR^y)R^z$, $-(C=S)N(R^y)R^z$, $-NH_2$, C_{1-4} alkoxy optionally mono-substituted with R^q, R^x as defined above, C_{1-4} alkyl optionally mono-substituted on an alpha carbon or higher by one of the substituents a)-ae) as defined for R^a;

M is selected from:

i) hydrogen;
ii) a pharmaceutically acceptable esterifying group or removable carboxyl protecting group; or
iii) an alkali metal or other pharmaceutically acceptable cation.

The present invention also provides novel carbapenem intermediates of the formula:



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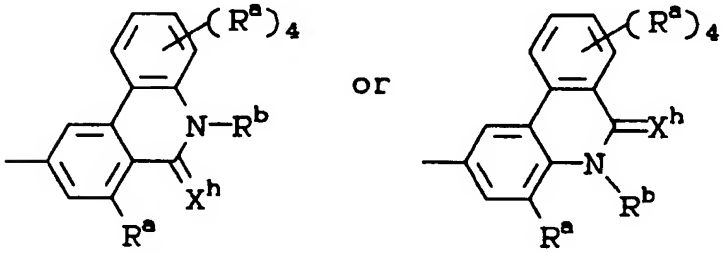
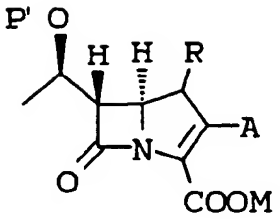


wherein:

R is H or CH_3;
X^h is O or S;
R^a and R^b are defined above, with the proviso that R^q additionally includes OP' where P' is defined below, that M^a and M^b of R^q both include M and that the Type d) hydroxy substituent and R^b additionally may be protected hydroxy, OP';
P' is a removable protecting group for hydroxy; and
M is a removable protecting group for carboxy.

Preferred intermediates have the formula:



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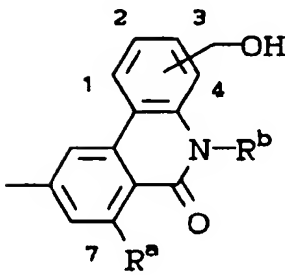
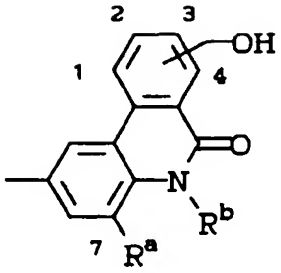


or



wherein

R is H or CH_3;

P' is a removable protecting group for hydroxy;

M is a removable protecting group for carboxy;

R^a is selected from the group consisting of H, OP', Cl, Br, I, SCH_3, CN, CHO, $SOCH_3$, SO_2CH_3, CO_2M, CH_2OP' or $CONH_2$;

R^b is H, OP', CH_2SCH_3, CH_2CN, CH_2CHO, CH_2SOCH_3, $CH_2SO_2CH_3$, CH_2CO_2M, CH_2OP', CH_2CH_2OP' or CH_2CONH_2; and

with the proviso that the -CH_2-OH substituent is in the 3- or 4-position of the phenanthridone.

DETAILED DESCRIPTION OF THE INVENTION

The manufacture of compounds of Formula I may be carried out in a three-stage synthesis scheme followed by a final step which allows for the removal of any protecting groups. The objective of the first synthetic stage is to produce a base phenanthridonyl compound which may be converted to the two-position substituent of the carbapenem of Formula I. The objective of the second synthetic stage is to attach the base phenanthridonyl to the carbapenem. Finally, the objective of the third synthetic stage is to substitute the phenanthridonyl with the desired R^a and R^b. This third synthetic stage may be performed after the first synthetic stage or during or after the second synthetic stage according to the nature of the various R^a and R^b.

Flow Sheets A1 and A2 demonstrate a suggested first stage synthesis. Flow Sheets B and C demonstrate two alternative second stage syntheses. The third synthesis varies according to the selected R^a and R^b.

The suggested first synthesis herein, Flow Sheets A1 and A2, can be generally described as a directed ortho metalation reaction to prepare starting materials required for a Suzuki cross-coupling reaction and finally ring closure to produce the desired phenanthridone platform. This suggested first synthesis is utilized to produce similar phenanthridone compounds by Snieckus, V., Chem. Rev. 1990, 90, 879-933; Fu. J.M. and Snieckus, V., Tet. Lett. 1990, 31, p. 1665; Siddiqui, M.A., et al., Tetrahedron Letters, Vol. 29, No. 43, 5463-5466 (1988); Mills, R.J., et al., J. Org. Chem., 1989, 54, 4372-4385; Mills, R.J., J. Org. Chem., 1989, 54, 4386-4390; Fu, J.M., et al., Tetrahedron Letters, Vol. 31, No. 12, pp 1665-1668 (1990); and Suzuki, A., et al., N., Synthetic Communications, 11(7), 513-519 (1981).

Referring to Flow Sheet A1 compound A1-1 is substituted with a directed metalation group (DMG) by methods according to Snieckus, et al., above. The function of the directed metalation group (DMG) is to orchestrate adornment of the aromatic ring. It is highly desirable of the DMG that it also provide a precursor substituent for the necessary carboxy function or amino function forming the amide linkage of the object phenanthridone. Suitable DMG to serve as a carboxyl precursor are secondary and tertiary amides and oxazolino groups. Specifically, these precursors may be, for example, -$CONEt_2$, -CONHMe, 4,4-dimethyl-2-oxazolinyl, and the like. In the instance of compound A1-1, DMG is of the carboxyl precursor type. Suitable DMG to serve as an amino precursor are protected primary and secondary amines. Specifically, these precursors may be -NH-t-Boc, -NH-pivaloyl, phenylsulfonamido, and the like. Compound A2-1 as described below is by way of example, of the

amino precursor type.

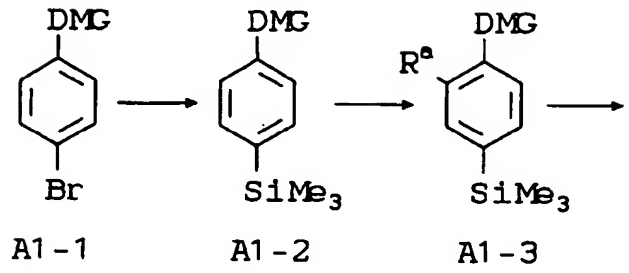
As the first step of flow Sheet A1, the bromine of compound A1-1 is protected through silylation via halogen metal exchange in the presence of TMS chloride at between about -100 to -50°C to produce aryl silane A1-2. Incorporation of an ortho substitutent R^a or its appropriate precursor may be made on compound A1-2 in accordance with standard directed metalation procedures described by Snieckus, et al., above. The resultant substituted aryl silane A1-3 is iteratively ortho metalated and treated with an appropriate boron containing electrophile to obtain the requisite aryl boronic acid A1-4. Suitable boron containing electrophiles include lower alkyl borates, such as trimethyl borate and tri-i-propyl borate. Alternatively, and not shown in the Flow Sheets, the ortho metalated compound may be treated with electrophiles such as trialkyltin halides providing the corresponding aryl stannanes which in turn are also useful intermediates in the production of biphenyls as reported by Stille, et al., J. Am. Chem. Soc., 1987, Vol. 109, page 5478-5486. Preparation of biphenyl intermediate A1-6 is accomplished in the Flow Sheets utilizing the Suzuki cross-coupling procedure and the appropriately adorned aryl compounds A1-4 and A1-5. The Suzuki coupling can be generally described as the reaction of an aryl boronic acid with an aryl halide or halide equivalent employing tetrakis(triphenylphosphine) palladium(0) catalyst in the presence of an aqueous solution of sodium carbonate in the solvents toluene/ethanol. The resulting biphenyl compound is isolated by standard methods. Compound A1-5 may itself be produced by standard methods to obtain the halogen substitution, X, the amino moiety $-NR'_2$ and the desired substituents R^a or their precursors. The preferred halogen X is bromine, iodine or the halogen equivalent trifluoromethanesulfonyloxy. The preferred amino moiety, $-NR'_2$, may be any of $-NO_2$, $-N_3$, protected amine or amine, substitued with R^b or its precursor. Biphenyl compound A1-6 is subsequently transformed into the halogenated biphenyl A1-7 via ipso substitution of the trimethylsilyl moiety in methylene chloride or other appropriate solvent employing iodine monochloride. Any number of halogenating reagents are suitable such IBr, NBS, I_2, Br_2, etc., which must be compatible with the already existing functionalities. Finally, the object compound, B1-1, is obtained via transamidizaton of the amino moiety with the latent carboxy precursor in the form of DMG.

Referring to Flow Sheet A2, the regio-isomeric phenanthridone B1-2, may be produced in a manner analogous to that of phenanthridone B1-1. Compound A2-1 is dissimilar to compound A1-4 in that DMG of compound A2-1 is of the amino precursor type. Compound A2-1 is reacted with the appropriately adorned compound A2-2 to prepare biphenyl intermediate A2-3 utilizing the Suzuki cross-coupling procedure. As above biphenyl compound A2-3 is transformed into halogenated biphenyl via ipso substitution A2-4 and finally into object phenanthridone B1-2 via transamidization.

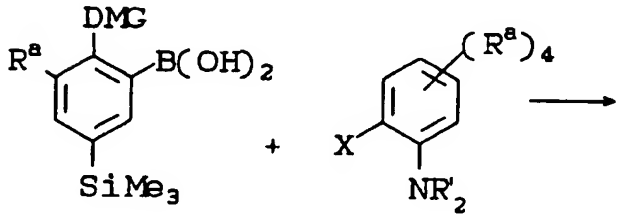
Presented with Flow Sheet A1 and A2, the skilled artisan will appreciate certain modification as possibly beneficial. In one modification, the ipso substitution of silicon to halogen might be performed after cyclization to form the object phenanthridone. In another modification, compounds A1-5 and A2-2 may be adorned utilizing a DMG substitutent replacing $-NR'_2$ and $-CO_2Me$ respectively. As above, the DMG substituent directs adornment of R^a or precursors thereof in manufacture. As above, the DMG should be of the carboxyl precursor type or amino precursor type as appropriate. In yet another modification, the oxocarbonyl of intermediate B1-1 or B1-2 can be converted to a thiocarbonyl to produce X^h as S, using Lawesson type reagents or by treating with phosphorus pentasulfide in an appropriate solvent. Another modification to produce X^h as S is to employ a carbon based DMG wherein the oxocarbonyl moiety is replaced by thiocarbonyl. A suitable carbon based DMG containing thiocarbonyl is -(C=S)NH-phenyl. Although compounds in which X^h is S are suitable, those in which X^h is O are preferred.

Although the foregoing method to produce phenanthridones B1-1 or B1-2 is preferred herein, there are of course other appropriate methods. In one method, phenanthridone, produced by procedures known in the art, is brominated at the 2-position as taught by Mosby, W.L., J. Chem. Soc., Vol. 76, pp 936 (1954). The 2-bromophenanthridone may also be obtained by the procedure of Walls, L.P., J. Chem. Soc., pp. 1406 (1935). Preparation of N-substituted, 2-bromo-phenanthridones may be prepared as taught by Cookson, R.F., et al.,J. Heterocycl. Chem., (1979) 9, 475. Substituted phenanthridones are prepared by Beckmann rearrangement of substituted 9-oxofluorene oximes by the method of Pan, H.-L., and Fletcher, T.L., J. Med. Chem., Vol. 12, pp. 822 (1969). Substituted phenanthridones are prepared by a Schmidt rearrangement of substituted 9-oxoflurorene by the method of Pan, H.-L., and Fletcher, T.L., J. Heterocycl. Chem., Vol. 7, pp 313 (1970). Substituted phenanthridones are discussed generally by Keene, B.R.T. and Tissington, P., Adv. Heterocyclic Chem., Vol. 13, pp 315 (1971).

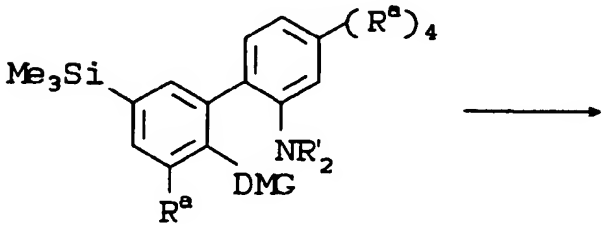
FLOW SHEET A1



A1-1 A1-2 A1-3

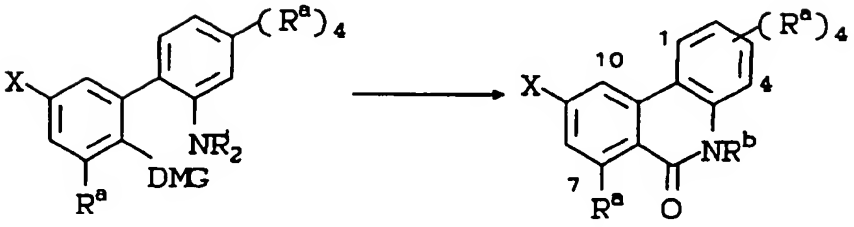


A1-4 A1-5



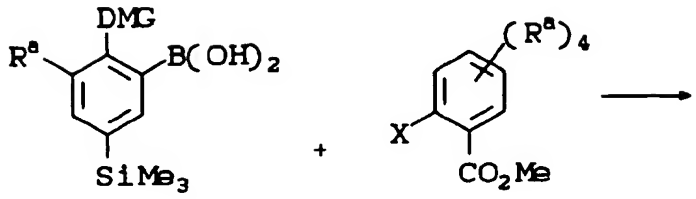
A1-6

FLOW SHEET A1 cont'd

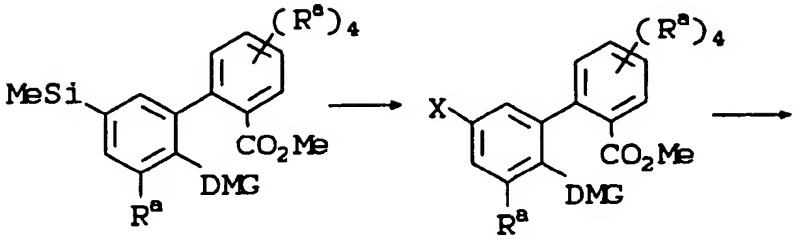


A1-7 B1-1

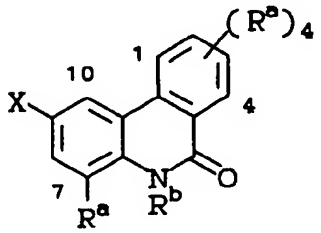
FLOW SHEET A2



A2-1 A2-2



A2-3 A2-4



B1-2

The object compound of Flows Sheet A1 and A2, phenanthridone B1-1 and B1-2, forms the nucleus of the 2-position substitution of the carbapenem compounds taught herein. As such it is shown to be R^a and R^b substituted. However, it is immediately clear to those skilled in the art that certain R^a and R^b listed above, if substituted on compounds A1-1, A1-5, A2-1 or A2-2 would not survive or permit the synthesis to compounds B1-1 or B1-2. Thus, where a certain R^a or R^b is desired on compound B1-1 or B1-2 and this R^a or R^b is not compatible with the synthesis scheme to produce, B1-1 or B1-2 then a compatible precursor substituent may be employed through the synthesis.

The identity of the precursor substituent employed is not crucial so long as it does not interfere with the synthesis to B1-1 or B1-2 and so long as it may be thereafter converted to more desireable substituent. Preferred precursor substituents for R^a are methyl, hydroxymethyl and protected hydroxymethyl. Preferred precursor substituents for R^b are 2-hydroxyethyl or protected 2-hydroxyethyl.

Thus, as to the R^a substituent on compound B1-1 or B1-2, it maybe an R^a with or without protecting groups stable to the conditions of producing compound B1-1 or B1-2, and stable to the conditions of subsequently adding B1-1 or B1-2, to the carbapenem. Alternatively, it may be a stable precursor substituent which is stable to the conditions of making B1-1 or B1-2, which is optionally stable to the conditions of adding B1-1 or B1-2, to the carbapenem and which is convertible to a desired R^a or to another precursor substituent.

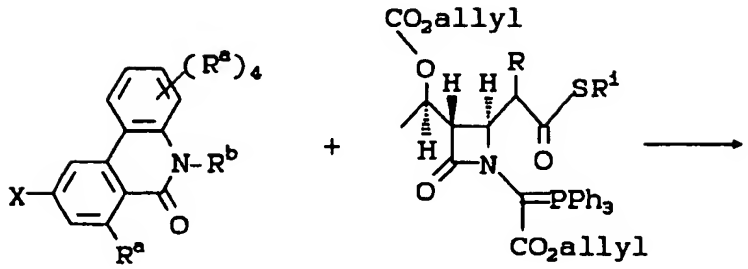
As stated above, the second stage synthesis is to attach the base phenanthridone B1-1 or B1-2 to the 2-position of the carbapenem. With stable R^a and R^b or suitable precursor substituents therefor, phenanthridone B1-1 or B1-2 may be added to azetidin-2-one B2 in a Grignard reaction as shown in Flow Sheet B. The Grignard

reaction requires that B1-1, for example, be converted to a Grignard reagent by reaction with magnesium and 1,2-dibromoethane in THF from 20°C to 60°C and subsequently contacting B1-1 as a Grignard reagent with B2 in THF at from -70°C to about 20°C to produce azetidin-2-one B3. Alternatively, B1-1 may be reacted with t-butyllithium, n-butyllithium, or the like in THF at from -78° to -50°C followed by the addition of magnesium bromide to produce the same Grignard reagent. R^1 of B3 is in practice pyrid-2-yl but may clearly be a variety of substituents including aromatic and heteroaromatic substituents. Further R^1 might be for example phenyl, 2-pyrimidinyl or 2-thiazolyl.

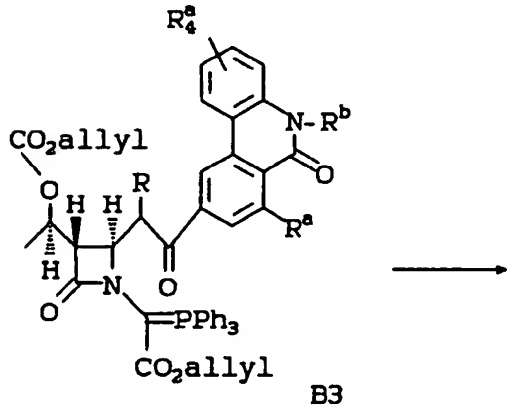
Azetidin-2-one B3 is an intermediate that may be ring closed to a carbapenem. It is on this intermediate that R^a, R^b or precursor substituents may be modified where such modification is incompatible with the carbapenem nucleus.

Compound B3 may be ring closed to carbapenem B4 by refluxing in xylene with a trace of p-hydroquinone for about 1 to 2 hours in an inert atmosphere. It is on this intermediate that final elaboration of R^a from a precursor substituent, e.g. hydroxymethyl, may be accomplished. Removal of the carboxyl and hydroxyl protecting groups then provides the final compound of Formula I. Such final elaboration and deprotection is described in further detail below.

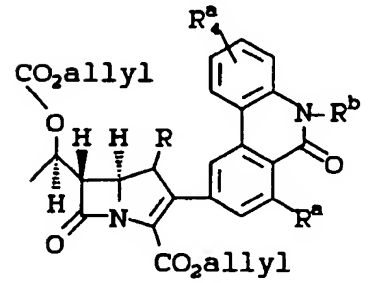
FLOW SHEET B



B1-1 B2



B3



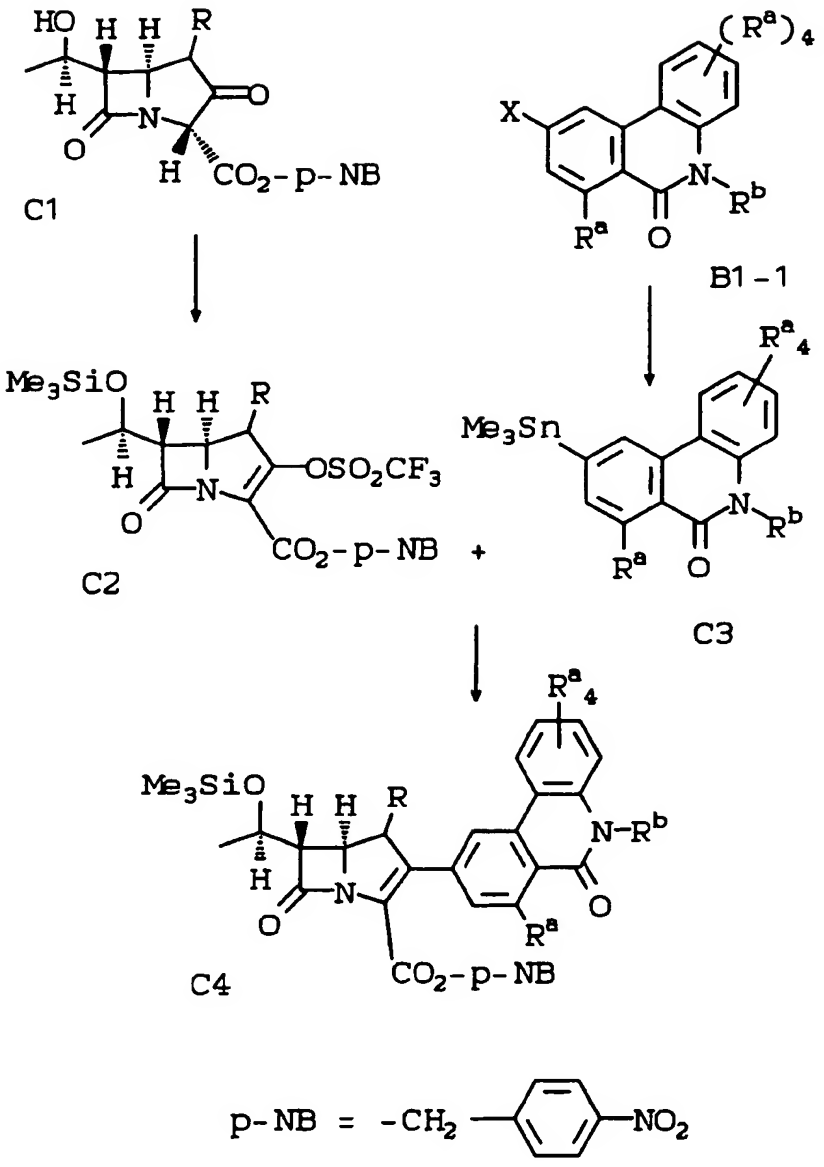
B4

Flow Sheet C shows an alternative preferred second stage synthesis, i.e. attachment of the base phenanthridone such as B1-1 to the 2-position of the carbapenem. This synthesis involves a palladium catalyzed cross-coupling reaction between a carbapenem triflate and a suitably substituted arylstannane, a process which is described in U.S. Pat. Appl. 485,096 filed February 26, 1990, corresponding to EP-A-0444889. In order to apply this synthesis, it is first necessary to modify phenanthridone B1-1 to the trimethylstannyl-phenanthridone C3. This is accomplished by reacting B1-1 with t-butyllithium in THF at from -78° to -50°C followed by the addition of trimethyltin chloride. Alternatively, phenanthridone B1-1 may be reacted with hexamethylditin in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium in an inert solvent such as toluene at from 25° to 110°C for from 0.25-24 hours to provide the same stannane C3. Referring to Flow Sheet C, the 2-oxocarbapenam C1 is reacted with a suitable trifluoromethanesulfonyl source, such as trifluoromethanesulfonic

anhydride, trifluoromethanesulfonyl chloride and the like, in the presence of an organic nitrogen base, such as triethylamine, diisopropylamine and the like, in polar aprotic solvent, such as tetrahydrofuran or methylene chloride. Optionally, an organic nitrogen base, such as triethylamine and the like, is then added to the reaction solution followed immediately by a silylating agent, such as trimethylsilyl trifluoromethanesulfonate to provide intermediate C2. An aprotic polar coordinating solvent, such as DMF, 1-methyl-2-pyrrolidinone and the like, is added. This is followed by the addition of a palladium compound, such as tris(dibenzylideneacetone)dipalladium-chloroform, palladium acetate and the like, optionally, a suitably substituted phenylphosphine, such as tris(4-methoxyphenyl)phosphine, tris(2,4,6- trimethoxyphenyl)phosphine and the like, and the stannane C3. A halide, source such as lithium chloride, zinc chloride or ammonium chlorides and the like, is added and the reaction solution is allowed to warm and is stirred at a suitable temperature, such as 0° to 50°C for from a few minutes to 48 hours. The carbapenem C4 is obtained by conventional isolation/purification methodology known in the art.

Generally speaking, the milder conditions of the synthesis shown in Flow Sheet C allow for a wider range of functional groups R^a or R^b to be present than the synthesis illustrated in Flow Sheet B. However, in certain cases it is advantageous for the R^a or R^b substituent(s) of the stannane C3 to be introduced in a protected or precursory form. Final elaboration of R^a or R^b from a precursor substituent, e.g. hydroxymethyl, may be accomplished on carbapenem intermediate C4. Removal of hydroxyl and carboxyl protecting groups then provides the final compound of Formula I. Such final elaboration and deprotection is described in further detail below.

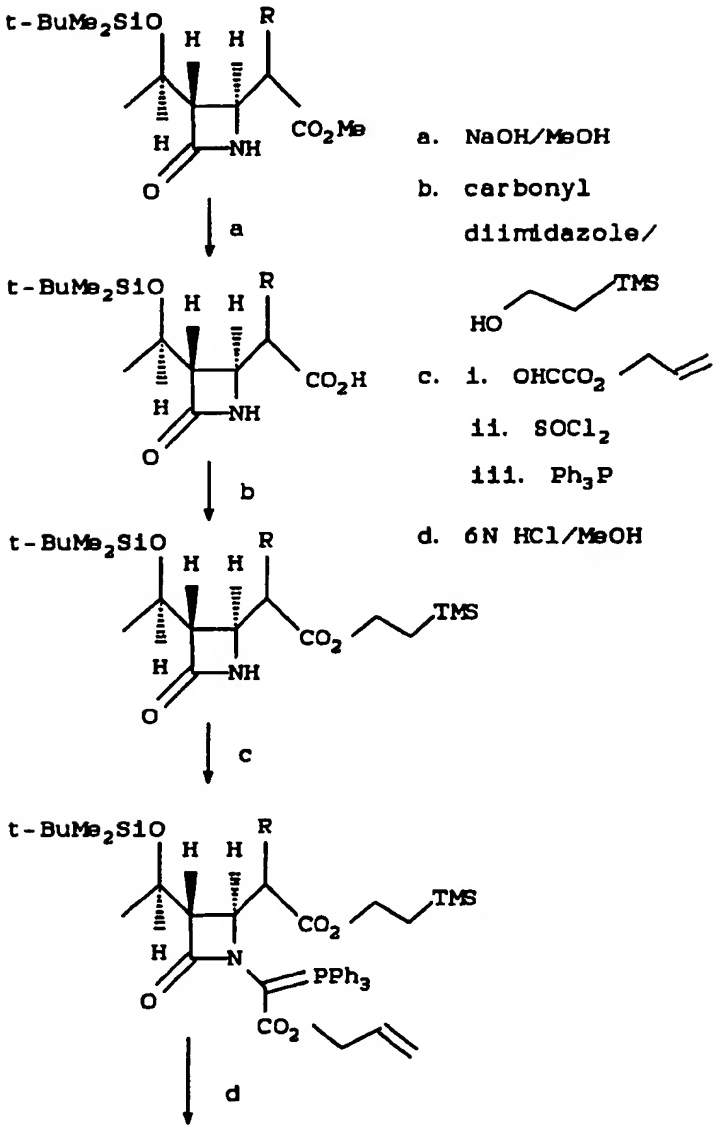
FLOW SHEET C



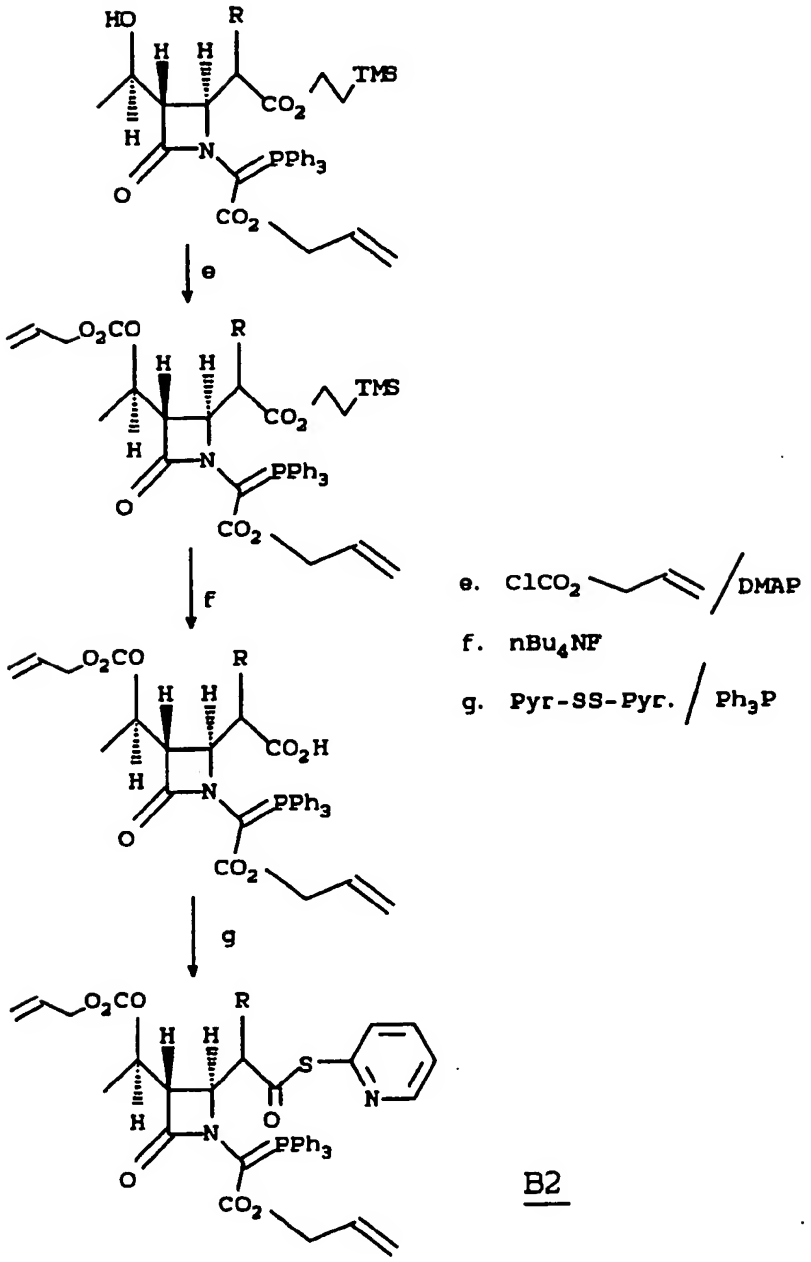
p-NB = $-CH_2-C_6H_4-NO_2$

Azetidin-2-one B2, a pyridyl-thioester, is a well known compound in the production of carbapenems. Diverse synthetic schemes useful to make B2 may be imagined by the skilled artisan. Particularly useful to the instant invention is a synthetic scheme set out further in Flow Sheet D below in which the symbol R is as defined above. The steps for preparing intermediate B2 are analogous to the procedures described, for example, in U.S. Pat. Nos. 4,260,627 and 4,543,257; L.D. Cama et al. Tetrahedron, 39, 2531 (1983); R.N. Guthikonda et al. J. Med. Chem., 30, 871 (1987) hereby incorporated by reference.

FLOW SHEET D


t-BuMe2SiO
H
H
R
CO2Me
NH
O
a
CO2H
b
TMS
HO
OHCCO2
SOCl2
Ph3P
c
d
N
PPh3
a. NaOH/MeOH
b. carbonyl diimidazole/
c. i.
ii.
iii.
d. 6N HCl/MeOH

FLOW SHEET D cont'd



The steps for preparing the 2-oxocarbapenam intermediate C1 are well known in the art and are explained in ample detail by D.G. Melillo et al., Tetrahedron Letters, 21, 2783 (1980), T. Salzmann et al., J. Am. Chem. Soc., 102, 6161 (1980), and L. M. Fuentes, I. Shinkai, and T. N. Salzmann, J. Am. Chem. Soc., 108, 4675 (1986). The syntheses are also disclosed in U.S. Pat. No. 4,269,772, U.S. Pat. No. 4,350,631, U.S. Pat. No. 4,383,946 and U.S. Pat. No. 4,414,155 all assigned to Merck and Company, Inc. and hereby incorporated by reference.

The general synthesis description depicted above in the Flow Sheets shows a protected 1-hydroxyethyl substitution on the 6-position of the carbapenem. After final deprotection, a 1-hydroxyethyl substituent is obtained, which is preferred in most cases. However, it has been been found that with certain 2-side-chain selections, the ultimate balance of favorable properties in the overall molecule may be enhanced by selection of

the 6-(1-fluoroethyl) moiety Instead. Preparation of 6-fluoroalkyl compounds within the scope of the present invention is carried out in a straightforward manner using techniques well known in the art of preparing carbapenem antibacterial compounds. See, e.g., J. G. deVries et al., Heterocycles, 23 (8), 1915 (1985); BE 900 718 A (Sandoz) and Japanese Patent Pub. No. 6-0163-882-A (Sanruku Ocean).

In preferred compounds of Formula I, R^1 is hydrogen. More preferably, R^1 is hydrogen and R^2 is (R)-$CH_3CH(OH)$- or (R)-$CH_3CH(F)$-. In the most preferred case, R^1 is hydrogen and R^2 Is (R)-$CH_3CH(OH)$-. While R = H is usually preferred, there are instances in which R = CH_3 may provide improved chemical stability, water solubility, or pharmacokinetic behavior. The substituent R = CH_3 may be of either configuration, i.e., the α or β-stereoisomer. Additionally, in preferred compounds, at least R^a in the 3- or 7-position of the phenanthridone is other than hydrogen. In the most preferred compounds, in total, two R^a and R^b substituents is other than hydrogen.

Suitable R^a and R^b are described above in the text associated with Formula I. Among preferred R^a are C_{1-4} alkyl mono-substituted with hydroxy, such as, hydroxymethyl; formyl; alkoxycarbonyl, such as, -$COOCH_3$; carbamoyl, such as, -$CONH_2$; hydroxoximinomethyl, such as, -CH=NOH or cyano. Among preferred R^b are hydroxymethyl, hydroxyethyl, -CH_2CHO, -CH_2COOCH_3, -CH_2CONH_2, -CH_2CH=NOH and -CH_2CN.

In regard to this preferred substitution, a hydroxyethyl group may be obtained for R^b of the phenanthridone as shown in Flow Sheets A1 and A2. In Flow Sheet A1, for instance, compound A1-5 may be substituted with -$NH(CH_2CH_2OH)$ or its appropriately protected equivalent where an appropriate protecting group is for,example t-butyldiphenylsilyl. Alternatively, for instance, in Flow Sheet A2, the DMG group might be -NH(^{t}BOC) which is removed under acid conditions from compound A2-4 which subsequently cyclizes to compound B1-2 where R^b is hydrogen. The nitrogen moiety of compound B1-2 may be alkylated using sodium hydride in appropriate solvent with 2-bromo-t-butyldiphenylsilylethanol to obtain R^b as protected hydroxyethyl. A hydroxymethyl may be obtained in any of positions 7, 1, 2, 3 or 4 for R^a as follows. As one method, hydroxymethyl may be substituted on any of rings A1-4 and A1-5 or A2-1 and A2-2 by standard procedures and appropriately protected. Alternatively, methyl, as a precursor substituent, is substituted on starting materials A1-4 and A1-5 or A2-1 and A2-2 in the appropriate positions by well know means and the starting materials reacted to a corresponding methyl-substituted B1-1 or B1-2 according the Flow Sheet A. Subsequently, the methyl substituent(s) of methyl-substituted B1-1 or B1-2 may be oxidized to bromomethyl with N-bromosuccinimide. This oxidation of the precursor substituent, methyl, is advantageously performed prior to substituting the phenanthridone on the azetidin-2-one as the oxidizing conditions are incompatible with either the azetidin-2-one or the subsequent carbapenem. In the case of the bromomethyl substituent, conversion to an hydroxymethyl substituted B1-1 or B1-2 may be accomplished by a three-step sequence. Reaction of the bromomethyl compound with potassium acetate in DMF at 80°C gives the corresponding acetoxymethyl compound. Removal of the acetate group, e.g. by hydrolysis with methanolic sodium hydroxide or by reduction with diisobutylaluminium hydride in THF, gives the hydroxymethyl substituted compound B1-1 or B1-2. Further elaboration of of hydroxymethyl substituted B1-1 or B1-2 according to Flow Sheet B produces a corresponding B3 and B4.

The preferred formyl substitution on the phenanthridone may be obtained on B4 from the hydromethyl substitution, in the case of R^a, or hydroxyethyl substitution in the case of R^b, by a Swern oxidation. For example, B4 is oxidized in methylene chloride at from -70°C to room temperature employing oxalyl chloride-dimethyl sulfoxide followed by triethylamine as the active agent. Obviously, the position of the resultant formyl substitution will depend upon the position of the hydroxymethyl or hydroxyethyl substitution B4.

The preferred -CH=NOH substitution on the phenanthridone may be conveniently obtained from the formyl substitution just described. This is accomplished simply by exposing the formyl substituted compound to hydroxylamine in an appropriate solvent at room temperature.

The preferred cyano substitution on the phenanthridone may be obtained from the -CH=NOH substitution just described. The -CH=NOH substituted compound is dehydrated with triflic anhydride and triethylamine in a solvent at -70°C.

The preferred -$COOCH_3$ substitution on the phenanthridone may be obtained from the hydromethyl or hydroxyethyl substituted B3 described above. For example, compound B3 is oxidized with Jones reagent to convert the hydroxymethyl substituent to the carboxylic acid group. The oxidation with Jones reagent may be incompatible with the carbapenem and thus is optimally performed before ring closure. Prior to ring closure, the carboxylic acid group Is esterified by sequentially contacting with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1-hydroxybenzotriazole, and methanol in an organic solvent at room temperature. Substituted esters may of course be obtained by replacing methanol with the corresponding substituted alcohol. Alternatively, a methyl substituted B1-1 or B1-2, as described above, may be oxidized with chromium trioxide or ^{n}Bu$_4$NMnO$_4$ to form carboxy.

The preferred carbamoyl substitution on the phenanthridone, may be obtained from B3 by oxidizing the

hydroxymethyl or hydroxyethyl group with Jones reagent to the corresponding carboxylic acid group as described above. This carboxylic acid substituent is converted to the carboxamide group, $-CONH_2$, by sequentially contacting with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1-hydroxybenzotriazole, and ammonia in an organic solvent at room temperature. Substituted amides may of course be obtained by replacing ammonia with the corresponding substituted amine.

Compounds substituted with the preferred R^a or R^b just described may also be obtained by employing the synthesis shown in Flow Sheet C. In this case, the synthetic transformations just described may be carried-out on intermediate C3 prior to attachment of the phenanthridone side chain to the carbapenem or on C4 after such attachment.

In the preparation methods described above, the carboxyl group at the 3-position and the hydroxyl group at the 8-position of the carbapenem remain blocked by protecting groups until the penultimate product is prepared. Suitable hydroxyl protecting groups, P', are silyl groups such as trialkylsilyl, aryl(alkyl)alkoxysilyl, alkoxydiarylsilyl and diarylalkylsilyl and carbonate groups such as alkyloxycarbonyl, substituted alkyloxycarbonyl, benzyloxycarbonyl, substituted benzyloxycarbonyl, allyloxycarbonyl and substituted allyloxycarbonyl. The preferred protecting groups, in addition to or including those shown in the schemes, are t-butylmethoxyphenylsilyl, t-butoxydiphenylsilyl, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, benzyloxycarbonyl, t-butyloxycarbonyl, 2,2,2-trichloroethyloxycarbonyl and allyloxycarbonyl. Suitable carboxyl protecting groups, M, in addition to or including those shown in the schemes are described herein below.

Deblocking may be carried out in a conventional manner. For compounds prepared according to Flow Sheet B, deprotection may be carried out in a palladium catalyzed rection in a solution containing potassium 2-ethylhexanoate and 2-ethylhexanoic acid or, alternatively, another suitable nucleophile such as pyrrolidine. Alternatively, for those prepared via Flow Sheet C, deprotection is conducted sequentially. Thus, compound C4 is exposed initially to aqueous acidic conditions, acetic acid or dilute HCl or the like, in an organic solvent such as tetrahydrofuran at 0°C to ambient temperature for from a few minutes to several hours. The resulting desilylated carbapenem may be isolated by conventional techniques, but is more conveniently taken into the final deprotection process. Thus, addition of an inorganic base such as $NaHCO_3$ or $KHCO_3$ and 10% Pd/C followed by hydrogenation provides for the removal of the p-nitrobenzyl protecting group and the formation of the final compound of Formula I.

With reference to the above definitions, "alkyl" means a straight or branched chain aliphatic hydrocarbon radical.

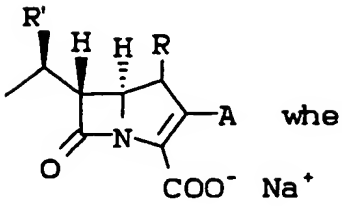
The term "heteroatom" means N, S, or O, selected on an independent basis.

The term "heteroaryl" has been defined herein, in relation to the R^x group, to have a specific and limited meaning, being only monocyclic. It is required that the monocyclic heteroaryl have at least one nitrogen atom, and optionally at most only one additional oxygen or sulfur heteroatom may be present. Heteroaryls of this type are pyrrole and pyridine (1 N); and oxazole, thiazole or oxazine (1 N + 1 O or 1 S). While additional nitrogen atoms may be present together with the first nitrogen and oxygen or sulfur, giving, e.g., a thiadiazole (2N's + 1S), the preferred heteroaryls are those where only nitrogen heteroatoms are present when there is more than one. Typical of these are pyrazole, imidazole, pyrimidine and pyrazine (2 N's) and triazine (3 N's).

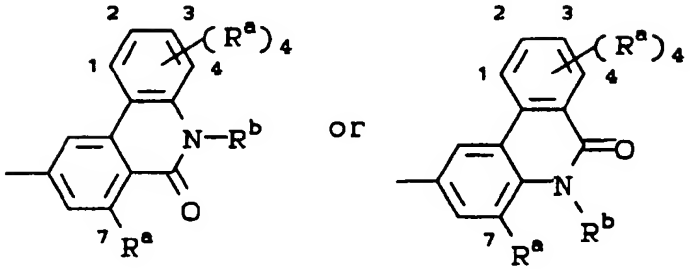
The heteroaryl group of R^x is always optionally mono-substituted by R^q, defined above, and substitution can be on one of the carbon atoms or one of the heteroatoms, although in the latter case certain substitutent choices may not be appropriate.

Listed in Tables I and II are specific compounds of the instant invention:

TABLE I



where R' is F or OH, R is H or Me and A is:



#	R^b	R^a	Ra position
1	-H	$-OCH_3$	7
2	-H	$-OCH_2CO_2CH_3$	7
3	-H	$-OCH_2CH_2OH$	4
4	-H	$-CF_3$	7
5	-H	-F	7,3,4
6	-H	-Cl	7,4
7	-H	-Br	7,4
8	-H	-I	7
9	-H	-OH	7,4
10	-H	$-OCOCH_3$	7
11	-H	$-OCONH_2$	7
12	-H	$-SCH_3$	7
13	-H	$-SOCH_3$	7
14	-H	$-SO_2CH_3$	7

#	R^b	R^a	Ra position
15	-H	$-SCH_2CH_2OH$	7
16	-H	$-SOCH_2CH_2OH$	4
17	-H	$-SCH_2CONH_2$	7
18	-H	$-SO_2NH_2$	7
19	-H	$-SO_2N(CH_3)_2$	3,4
20	-H	-NHCHO	7,4
21	-H	$-NHCOCH_3$	7
22	-H	$-NHCO_2CH_3$	7
23	-H	$-NHSO_2CH_3$	7
24	-H	-CN	7,3
25	-H	-CHO	7,4
26	-H	$-COCH_3$	7
27	-H	$-COCH_2OH$	4
28	-H	-CH=NOH	4
29	-H	$-CH=NOCH_3$	7
30	-H	$-CH=NOCH_2CO_2CH_3$	4
31	-H	$-CH=NOCMe_2CO_2CH_3$	3
32	-H	$-CH=NOCMe_2CONH_2$	7
33	-H	$-CO_2CH_2CH_2OH$	7
34	-H	$-CONH_2$	7,4
35	-H	$-CONHCH_3$	4
36	-H	$-CON(CH_3)_2$	7
37	-H	$-CONHCH_2CN$	7
38	-H	$-CONHCH_2CONH_2$	7
39	-H	$-CONHCH_2CO_2CH_3$	7
40	-H	-CONHOH	7
41	-H	$-CONHOCH_3$	4
42	-H	-tetrazolyl	7
43	-H	$-CO_2CH_3$	4
44	-H	$-SCF_3$	7

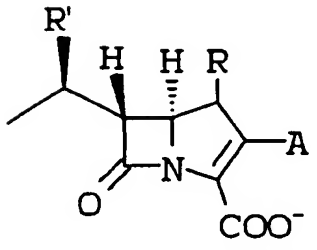
#	R^b	R^a	Ra position
45	-H	$-PO_2NH_2$	7
46	-H	$-CONHSO_2Ph$	7
47	-H	$-CONHSO_2NH_2$	7
48	-H	$-SO_2CF_3$	7
49	-H	$-SO_2NHCN$	7
50	-H	$-SO_2NHCONH_2$	7
51	-H	-CH=CHCN	7
52	-H	$-CH=CHCONH_2$	7
53	-H	$-CH=CHCO_2CH_3$	4
54	-H	$-C\equiv C-CONH_2$	7
55	-H	$-C\equiv C-CN$	4
56	-H	$-CH_2OH$	2
57	-H	$-CH_2N_3$	4
58	-H	$-CH_2CO_2CH_3$	4
59	-H	$-SO_2CH_2CH_2OH$	7
60	-H	$-CH_2I$	7
61	$-CH_2OCH_3$	$-OCH_3$	7
62	$-CH_2OCH_2CO_2CH_3$	$-OCH_2CO_2CH_3$	7
63	$-CH_2OCH_2CH_2OH$	$-OCH_2CH_2OH$	7
64	$-CH_2CF_3$	$-CF_3$	7
65	$-CH_2CH_2F$	-F	7
66	$-CH_2CH_2Cl$	-Cl	7
67	$-CH_2CH_2Br$	-Br	7
68	$-CH_2CH_2I$	-I	7
69	$-CH_2OH$	-OH	7
70	$-CH_2OCOCH_3$	$-OCOCH_3$	7
71	$-CH_2OCONH_2$	$-OCONH_2$	7
72	$-CH_2SCH_3$	$-SCH_3$	7
73	$-CH_2SOCH_3$	$-SOCH_3$	7
74	$-CH_2SO_2CH_3$	$-SO_2CH_3$	7

#	R^b	R^a	Ra position
75	$-CH_2SCH_2CH_2OH$	$-SCH_2CH_2OH$	7
76	$-CH_2SOCH_2CH_2OH$	$-SOCH_2CH_2OH$	7
77	$-CH_2SCH_2CONH_2$	$-SCH_2CONH_2$	7
78	$-CH_2SO_2NH_2$	$-SO_2NH_2$	7
79	$-SO_2N(CH_3)_2$	$-SO_2N(CH_3)_2$	7
80	$-CH_2CH_2NHCHO$	$-NHCHO$	7
81	$-CH_2CH_2NHCOCH_3$	$-NHCOCH_3$	7
82	$-CH_2CH_2NHCO_2CH_3$	$-NHCO_2CH_3$	7
83	$-CH_2CH_2NHSO_2CH_3$	$-NHSO_2CH_3$	7
84	$-CH_2CN$	$-CN$	1
85	$-CH_2CHO$	$-CHO$	7
86	$-CH_2COCH_3$	$-COCH_3$	7
87	$-CH_2COCH_2OH$	$-COCH_2OH$	7
88	$-CH_2CH=NOH$	$-CH=NOH$	7
89	$-CH_2CH=NOCH_3$	$-CH=NOCH_3$	7
90	$-CH_2CH=NOCH_2CO_2CH_3$	$-CH=NOCH_2CO_2CH_3$	7
91	$-CH_2CH=NOCMe_2CO_2Me$	$-CH=NOCMe_2CO_2CH_3$	7
92	$-CH_2CH=NOCMe_2CONH_2$	$-CH=NOCMe_2CONH_2$	7
93	$-CH_2CO_2CH_2CH_2OH$	$-CO_2CH_2CH_2OH$	7
94	$-CH_2CONH_2$	$-H$	*
95	$-CH_2CONHCH_3$	$-H$	*
96	$-CH_2CON(CH_3)_2$	$-H$	*
97	$-CH_2CONHCH_2CN$	$-H$	*
98	$-CH_2CONHCH_2CONH_2$	$-H$	*
99	$-CH_2CONHCH_2CO_2Me$	$-H$	*
100	$-CH_2CONHOH$	$-H$	*
101	$-CH_2CONHOCH_3$	$-H$	*
102	$-CH_2$tetrazolyl	$-H$	*
103	$-CH_2CO_2CH_3$	$-H$	*
104	$-CH_2SCF_3$	$-H$	*

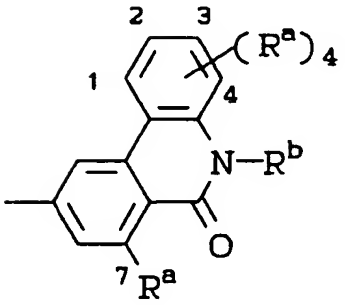
#	R^b	R^a	Ra position
105	$-CH_2PO_2NH_2$	-H	*
106	$-CH_2CONHSO_2Ph$	-H	*
107	$-CH_2CONHSO_2NH_2$	-H	*
108	$-CH_2SO_2CF_3$	-H	*
109	$-CH_2SO_2NHCN$	-H	*
110	$-CH_2SO_2NHCONH_2$	-H	*
111	$-CH_2CH=CHCN$	-H	*
112	$-CH_2CH=CHCONH_2$	-H	*
113	$-CH_2CH=CHCO_2CH_3$	-H	*
114	$-CH_2C\equiv C-CONH_2$	-H	*
115	$-CH_2C\equiv C-CN$	-H	*
116	$-CH_2CH_2OH$	-H	*
117	$-CH_2CH_2N_3$	-H	*
118	$-CH_2CH_2CO_2CH_3$	-H	*
119	$-CH_2SO_2CH_2CH_2OH$	-H	*
120	$-CH_2CH_2I$	-H	*
121	-OH	-H	*
122	$-OCH_3$	-H	*
123	$-CF_3$	-H	*
124	$-SO_2CH_3$	-H	*
125	$-SO_2NH_2$	-H	*
126	$-NH_2$	-H	*
127	-H	$-CONH_2$	7
128	-H	$-CONH_2$	4
129	-H	$-CONH_2$	3
130	-H	-CN	7
131	-H	-CN	4
132	-H	-CN	3
133	-H	-CHO	7
134	-H	-CHO	4

#	R^b	R^a	Ra position
135	-H	-CHO	3
136	-H	$-CH_2OH$	7
137	-H	$-CH_2OH$	4
138	-H	$-CH_2OH$	3
139	$-CH_2CN$	$-CONH_2$	7
140	$-CH_2CN$	-CHO	7
141	$-CH_2CN$	$-CH_2OH$	7
142	$-CH_2CN$	-H	*
143	$-CH_2CN$	-CN	7
144	$-CH_2CN$	$-CONH_2$	3
145	$-CH_2CN$	-CN	3
146	$-CH_2CN$	$-CH_2OH$	3
147	$-CH_2CN$	-CHO	3
148	$-CH_2CN$	$-CONH_2$	4
149	$-CH_2CN$	-CN	4
150	$-CH_2CN$	$-CH_2OH$	4
151	$-CH_2CN$	-CHO	4
152	-H	$-SCH_3$	4
153	-H	$-S(O)CH_3$	4
154	-H	$-SO_2CH_3$	4
155	-H	$-SCH_3$	3
156	-H	$-S(O)CH_3$	3
157	-H	$-SO_2CH_3$	3
158	-H	-Br	3
159	-H	-I	3
160	-H	-Br	4
161	-H	-I	4

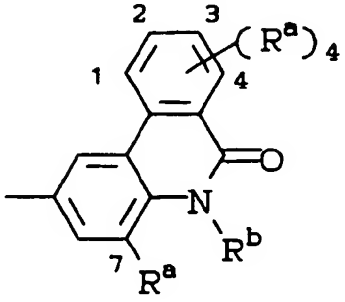
TABLE II



where R' is F or OH, R is H or Me, and A is:



or



#	R^b	R^a	
1	-H	4-CHO	7-$CONH_2$
2	-H	4-CN	7-$CONH_2$
3	-H	4-CH_2OH	7-$CONH_2$
4	-H	3-CHO	7-$CONH_2$
5	-H	3-CN	7-$CONH_2$
6	-H	3-CH_2OH	7-$CONH_2$
7	-H	3-CH_2OH	7-CN
8	-H	4-CH_2OH	7-CN
9	-H	4-CH_2OH	7-CN
10	-H	3-$CONH_2$	7-CN

The carbapenem compounds of the present invention are useful per se and in their pharmaceutically acceptable salt and ester forms in the treatment of bacterial infections in animal and human subjects. The term "pharmaceutically acceptable ester or salt" refers to those salt and ester forms of the compounds of the present invention which would be apparent to the pharmaceutical chemist, i.e. , those which are non-toxic and which would favorably affect the pharmacokinetic properties of said compounds, their palatability, absorption, distribution, metabolism and excretion. Other factors, more practical in nature, which are also important in the selection, are cost of the raw materials, ease of crystallization, yield, stability, hygroscopicity, and flowability of the resulting bulk drug. Conveniently, pharmaceutical compositions may be prepared from the active ingredients in combination with pharmaceutically acceptable carriers. Thus, the present invention is also concerned with pharmaceutical compositions and methods of treating bacterial infections utilizing as an active ingredient the novel carbapenem compounds of the present invention.

The pharmaceutically acceptable salts referred to above may take the form -COOM. The M may be an alkali

metal cation such as sodium or potassium. Other pharmaceutically acceptable cations for M may be calcium, magnesium, zinc, ammonium, or alkylammonium cations such as tetramethylammonium, tetrabutylammonium, choline, triethylhydroammonium, meglumine, triethanolhydroammonium, etc.

The pharmaceutical acceptable esters of the novel carbapenem compounds of the present invention are such as would be readily apparent to a medicinal chemist, and include, for example, those described in detail in U.S. Pat. No. 4,309,438, Column 9, line 61 to Column 12, line 51, which is incorporated herein by reference. Included within such pharmaceutically acceptable esters are those which are hydrolyzed under physiological conditions, such as pivaloyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, and those described in detail in U.S. Pat. No. 4,479,947, which is incorporated herein by reference.

The novel carbapenem compounds of the present invention may take the form COOM, where M is a readily removable carboxyl protecting group. Such conventional blocking groups consist of known ester groups which are used to protectively block the carboxyl group during the synthesis procedures described above. These conventional blocking groups are readily removable, i.e., they can be removed, if desired, by procedures which will not cause cleavage or other disruption of the remaining portions of the molecule. Such procedures include chemical and enzymatic hydrolysis, treatment with chemical reducing or oxidizing agents under mild conditions, treatment with a transition metal catalyst and a nucleophile, and catalytic hydrogenation. Broadly, such ester protecting groups include alkyl, substituted alkyl, benzyl, substituted benzyl, aryl, substituted aryl, allyl, substituted allyl and triorganosilyl. Examples of specific such ester protecting groups include benzhydryl, p-nitrobenzyl, 2-naphthylmethyl, allyl, 2-chloroallyl, benzyl, t-butyl, 2,2,2-trichloroethyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, trimethylsilyl, 2-(trimethyl)silylethyl, phenacyl, p-methoxybenzyl, acetonyl, o-nitrobenzyl, p-methoxyphenyl and 4-pyridylmethyl.

The compounds of the present invention are valuable antibacterial agents active against various Gram-positive and to a lesser extent Gram-negative bacteria and accordingly find utility in human and veterinary medicine. The antibacterials of the invention are not limited to utility as medicaments; they may be used in all manner of industry, for example: additives to animal feed, preservation of food, disinfectants, and in other industrial systems where control of bacterial growth is desired. For example, they may be employed in aqueous compositions in concentrations ranging from 0.1 to 100 parts of antibiotic per million parts of solution in order to destroy or inhibit the growth of harmful bacteria on medical and dental equipment and as bactericides in industrial applications, for example in waterbased paints and in the white water of paper mills to inhibit the growth of harmful bacteria.

The compounds of this invention may be used in any of a variety of pharmaceutical preparations. They may be employed in capsule, powder form, in liquid solution, or in suspension. They may be administered by a variety of means; those of principal interest include: topically or parenterally by injection (intravenously or intramuscularly).

Compositions for injection, a preferred route of delivery, may be prepared in unit dosage form in ampules, or in multidose containers. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents. Alternatively, the active ingredient may be in powder form for reconstitution, at the time of delivery, with a suitable vehicle, such as sterile water. Topical applications may be formulated in hydrophobic or hydrophilic bases as ointments, creams, lotions, paints, or powders.

The dosage to be administered depends to a large extent upon the condition and size of the subject being treated as well as the route and frequency of administration, the parenteral route by injection being preferred for generalized infections. Such matters, however, are left to the routine discretion of the therapist according to principles of treatment well known in the antibacterial art. Another factor influencing the precise dosage regimen, apart from the nature of the infection and peculiar identity of the individual being treated, is the molecular weight of the chosen species of this invention.

The compositions for human delivery per unit dosage, whether liquid or solid, may contain from 0.1% to 99% of active material, the preferred range being from about 10-60%. The composition will generally contain from about 15 mg to about 1500 mg of the active ingredient; however, in general, it is preferable to employ a dosage amount in the range of from about 250 mg to 1000 mg. In parenteral administration, the unit dosage is usually the pure compound I in sterile water solution or in the form of a soluble powder intended for solution.

The preferred method of administration of the Formula I antibacterial compounds is parenteral by i.v. infusion, i.v. bolus, or i.m. injection.

For adults, 5-50 mg of Formula I antibacterial compounds per kg of body weight given 2, 3, or 4 times per day is preferred. Preferred dosage is 250 mg to 1000 mg of the Formula I antibacterial given two (b.i.d.) three (t.i.d.) or four (q.i.d.) times per day. More specifically, for mild infections a dose of 250 mg t.i.d. or q.i.d. is recommended. For moderate infections against highly susceptible gram positive organisms a dose of 500 mg t.i.d. or q.i.d. is recommended. For severe, life-threatening infections against organisms at the upper limits of sen-

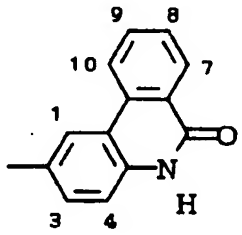
sitivity to the antibiotic, a dose of 1000 mg t.i.d. or q.i.d. is recommended.

For children, a dose of 5-25 mg/kg of body weight given 2, 3, or 4 times per day is preferred; a dose of 10 mg/kg t.i.d. or q.i.d. is usually recommended.

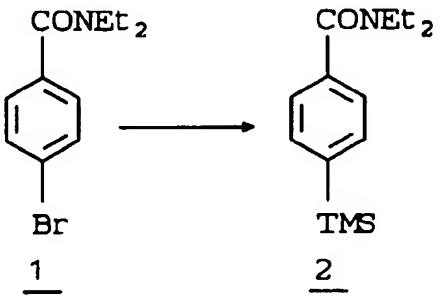
Antibacterial compounds of Formula I are of the broad class known as carbapenems or 1-carbadethiapenems. Naturally occuring carbapenems are susceptible to attack by a renal enzyme known as dehydropeptidase (DHP). This attack or degradation may reduce the efficacy of the carbapenem antibacterial agent. The compounds of the present invention, on the other hand, are significantly less subject to such attack, and therefore may not require the use of a DHP inhibitor. However, such use is optional and contemplated to be part of the present invention. Inhibitors of DHP and their use with carbapenem antibacterial agents are disclosed in the prior art [see European Patent Applications No. 79102616.4 filed July 24, 1979 (Patent No. 0 007 614); and No. 82107174.3, filed August 9, 1982 (Publication No. 0 072 014)].

The compounds of the present invention may, where DHP inhibition is desired or necessary, be combined or used with the appropriate DHP inhibitor as described in the aforesaid patents and published application. Thus, to the extent that the cited European patent applications 1.) define the procedure for determining DHP susceptibility of the present carbapenems and 2.) disclose suitable inhibitors, combination compositions and methods of treatment, they are incorporated herein by reference. A preferred weight ratio of Formula I compound: DHP inhibitor in the combination compositions is about 1:1. A preferred DHP inhibitor is 7-(L-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamide)-2-heptenoic acid or a useful salt thereof.

The second phenanthridone ring of Formula I is not numbered in this text and claims as convention dictates. In the examples, conventional numbering of this ring is employed per the formula:



EXAMPLE 1



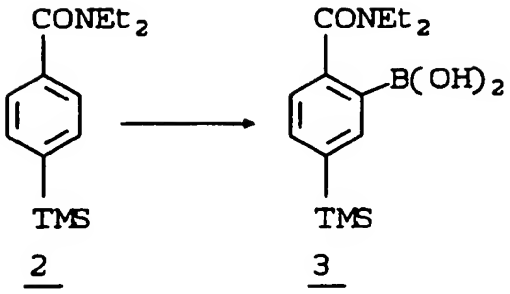
1 2

Chlorotrimethylsilane (10.4 mL, 81.9 mmol, 3.0 eq) was added to a stirred solution of 1 (7.0 g, 27.3 mmol) in dry THF (103 mL) at -78°C under N_2. Tert-butyllithium (23.1 mL, 30 mmol, 1.1 eq) was added dropwise at -78°C over 45 minutes. The reaction mixture was warmed to 0°C with an ice bath and then quenched with saturated ammonium chloride solution (25 mL). After removal of THF in vacuo the reaction mixture was poured into ether (400 mL) and washed with water, saturated sodium bicarbonate solution (2 x 50 mL), water, and brine. The ethereal layer was dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification using flash chromatography (20% EtOAc/hex) afforded 5.7 g (87%) of aryl silane 2, a white solid.

^{1}H-NMR for 2 [400 MHz, $CDCl_3$, rotamers]: δ 0.24 (s, 9H), 1.08 (broad s, 3H), 1.21 (broad s, 3H), 3.23 (broad s, 2H), 3.51 (broad s, 2H), 7.30 (d, J=8.1 Hz, 2H), 7.50 (d, J=8.1 Hz, 2H).

IR($CHCl_3$): 3010, 1615 cm^{-1}.

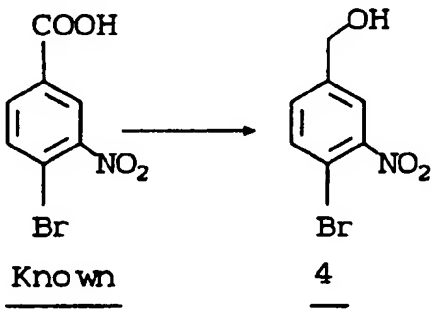
EXAMPLE 2



To a stirred solution of N,N,N',N'-tetramethylethylenediamine (2.7 mL, 17.6 mmol, 1.1 eq) in anhydrous THF (100 mL) at -78°C under N_2 was added dropwise sec-butyllithium (13.0 mL, 16.8 mmol, 1.05 eq). After 15 minutes the yellow mixture was treated with a solution of 2 (4.0 g, 16.0 mmol) in dry THF (40 mL), and the resultant red mixture was stirred for 1 hour at -78°C. Trimethylborate (2.0 mL, 17.6 mmol, 1.1 eq) was added dropwise. The reaction flask was warmed to 0°C with an ice bath and then stirred for 5 minutes. The green reaction mixture was quenched with 8% HCl solution (60 mL), stirred for 10 minutes, and the organic solvent concentrated in vacuo. The mixture was poured into ether and the ethereal layer was washed with water (2x), brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification using flash chromatography (5:3:1 EtOAc/acetone/H_2O) provided 3.77 g (80%) of boronic acid 3, a white foam.

^{1}H-NMR for 3 [200 MHz, $CDCl_3$, rotamers]: δ 0.27 (s, 9H), 0.88 to 1.16 (m, 6H), 3.27 to 3.36 (m, 4H), 7.28 (d, J=6.4 Hz, 1H), 7.52 (d, J=7.6 Hz, 1H), 8.15 (s, 1H). IR($CHCl_3$): 2960, 1615, 1601 cm^{-1}.

EXAMPLE 3

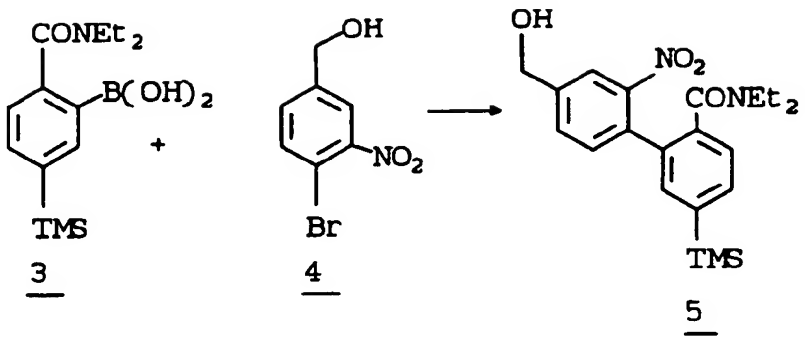


To a stirred solution of known bromo-nitrobenzoic acid (5.0 g, 20.3 mmol) in dry THF (40.6 mL) under N_2 at room temperature was added dropwise the borane-tetrahydrofuran complex (40.6 mL, 40.6 mmol, 2.0 eq). After stirring at reflux for 1 hour the reaction mixture was quenched with dropwise addition of triethylamine (1 mL) in methanol (50 mL) at 0°C. The solvent was then removed in vacuo to give crude 4. Purification using flash chromatography (30% EtOAc/hex) provided 4.5 g (96%) of 4, an off-white solid.

^{1}H-NMR for 4 [400 MHz, $CDCl_3$]: δ 1.86 (t, J=5.8 Hz, 1H), 4.74 (d, J=5.8 Hz, 2H), 7.41 (dd, J=8.3, 2.1 Hz, 1H), 7.70 (d, J=8.3 Hz, 1H), 7.85 (s, 1H).

IR($CHCl_3$): 3605, 3500 to 3200, 3010, 2880, 1605, 1535, 1355 cm^{-1}.

EXAMPLE 4



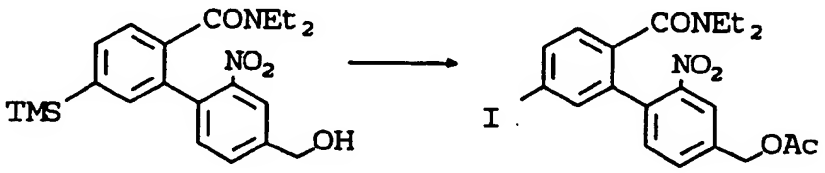
3 4 5

Aqueous sodium carbonate (8.7 mL, 17.4 mmol, 2.0 eq) was added to a stirred solution of 3 (2.0 g, 8.7 mmol) and tetrakis(triphenylphosphine) palladium (0) (502.8 mg, 5.0 mol%) in toluene (33.5 mL). The resulting two-phase mixture was stirred for 10 minutes under N_2 at room temperature. A solution of 4 (2.8 g, 9.6 mmol, 1.1 eq) dissolved in absolute ethanol (9.6 mL) was added, and the heterogeneous mixture was stirred for 3 hours at reflux under N_2. The cooled reaction mixture was poured into ether (175 mL) and washed with water (1X), saturated sodium carbonate solution (2 x 25 mL), water (1X), and brine. The organic layer was dried – ($MgSO_4$), filtered, and evaporated in vacuo. Purification using flash chromatography (60% EtOAc/hex) provided 2.9 g (83%) of the biphenyl compound 5, a yellow foam.

^{1}H-NMR for 5 [400 MHz, $CDCl_3$, rotamers]: δ 0.24 (s, 9H), 0.87 (t, J=7.1 Hz, 3H), 0.94 (t, J=7.1 Hz, 3H), 2.40 (broad s, 1H), 2.72 to 3.65 (broad, 4H), 4.76 (s, 2H), 7.30 to 7.32 (m, 2H), 7.51 to 7.56 (m, 3H), 7.93 (s, 1H).

IR($CHCl_3$): 3360, 3520 to 3300, 2990, 1620, 1605, 1530 cm^{-1}.

EXAMPLE 5



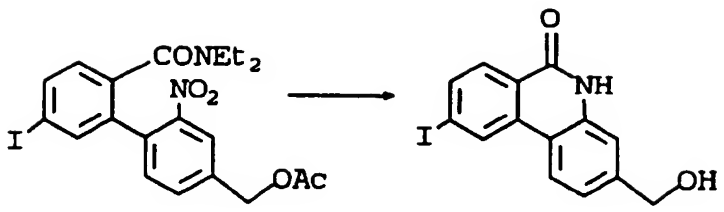
5 6

Acetic anhydride (6.8 mL, 72.4 mmol, 10.0 eq) was added to a stirred solution of 5 (2.9 g, 7.24 mmol) in dry pyridine (36 mL). The reaction mixture was stirred for 25 minutes at room temperature under N_2. The solvent was removed in vacuo and the residual oil azeotroped from toluene. The crude acetate was redissolved in dry dichloromethane (20 mL), and a 1.0 M solution of iodine monochloride in dichloromethane (33 mL, 33.3 mmol, 4.6 eq) was added dropwise over 1 hour using an addition funnel. The reaction mixture was then poured into ether (250 mL) and the organic layer was washed with saturated sodium thiosulfate solution (3 x 30 mL), water (1X), saturated sodium bicarbonate solution (1 x 30 mL), water (1X), and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo to afford 3.6 g (quantitative yield) of 6, a yellow oil.

^{1}H-NMR for 6 [400 MHz, $CDCl_3$, rotamers]: δ 0.81 (t, J=7.1 Hz, 3H), 0.98 (t, J=7.1 Hz, 3H), 2.14 (s, 3H), 2.78 to 3.65 (broad, 4H), 5.17 (s, 2H), 7.08 (d, J=8.1 Hz, 1H), 7.49 to 7.61 (m, 3H), 7.76 (d, J=8.0 Hz, 1H), 7.97 (s, 1H).

IR($CHCl_3$): 3010, 1745, 1610, 1530 cm^{-1}.

EXAMPLE 6



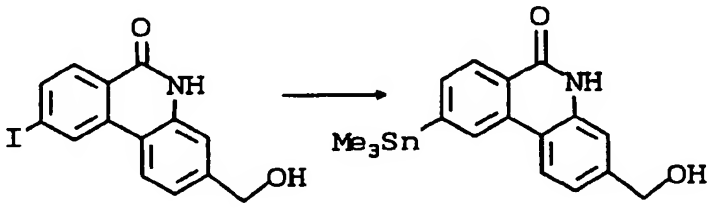
6 7

A solution of 25% sodium methoxide in methanol (0.53 mL, 2.4 mmol, 1.1 eq) was added to a stirred solution of 6 (1.1 g, 2.2 mmol) in dry methanol (11.0 mL). The reaction mixture was stirred for 10 minutes at room temperature under N_2. Acetic acid (6.0 mL) and dry tetrahydrofuran (11.0 mL) were then added. Iron powder (371.9 mg, 6.7 mmol, 3.0 eq) was added next, and the reaction mixture was stirred at reflux until a white solid had separated (approximately 15 minutes). The reaction mixture was cooled, poured into ice water (250 mL), and the solid filtered. The crude cyclized product was redissolved in hot ethanol (250 mL), filtered through a hot-sintered glass funnel, and the solvent removed in vacuo. Recrystallization from ethanol provided 501 mg (64%) of the cyclized amide 7, a white fluffy solid.

^{1}H-NMR for 7 [400 MHz, D_6 DMSO]: δ 4.57 (s, 2H), 5.36 (t, J=5.7 Hz, 1H), 7.16 (d, J=8.2 Hz, 1H), 7.33 (s, 1H), 7.93 (d, J=8.4Hz, 1H), 8.00 (d, J=8.4 Hz, 1H), 8.35 (d, J=8.4 Hz, 1H), 8.85 (s,1H), 11.74 (s,1H).

IR (KBr): 1670, 1601 cm^{-1}.

EXAMPLE 7



7 8

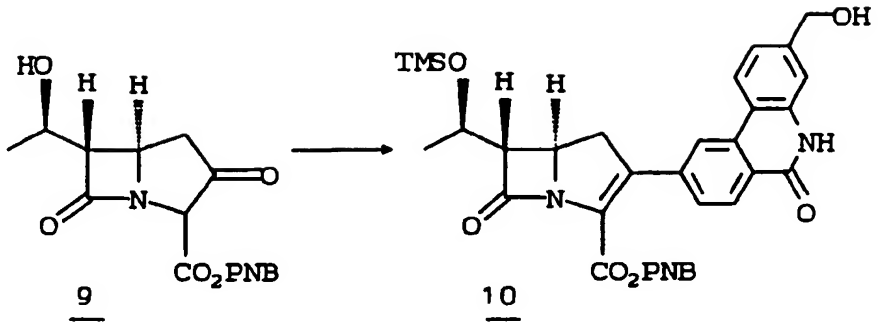
To a suspension of 7 (457 mg, 1.3 mmol) in toluene (45 mL) under N_2 was added hexamethylditin (0.28 mL, 1.43 mmol, 1.1 eq), tetrakis (triphenylphosphine) palladium (0) (75 mg, 5.0 mol%), and triphenylphosphine (10.2 mg, 3.0 mol%). After bubbling N_2 through the reaction mixture for 15 minutes, the reaction was heated to reflux for 1 hour under N_2. The reaction mixture was cooled, poured into ethyl acetate (175 mL), and washed with saturated sodium bicarbonate solution (2 x 25 mL), water (2x), and brine. The organic layer was dried – ($MgSO_4$), filtered, and evaporated in vacuo.

Recrystallization from acetone/hexane provided 469 mg (93%) of stannane 8, a white powder.

^{1}H-NMR for 8 [400 MHz, D_6 DMSO]: δ 0.37 (s,9H), 4.56 (s, 2H), 5.34 (t, J=5.7 Hz, 1H), 7.18 (d, J=8.3 Hz, 1H), 7.33 (s, 1H), 7.72 (d, J=7.7 Hz, 1H), 8.21 (d, J=7.7 Hz, 1H), 8.39 (d, J=8.4 Hz, 1H), 8.55 (s, 1H), 11.63 (s, 1H).

IR(KBr): 1650, 1601, 1540 cm^{-1}.

EXAMPLE 8



To a stirred solution of the bicyclic β-keto ester 9 (288.1 mg, 0.83 mmol) in dry THF (4.1 mL) at -78°C under N_2 was added diisopropylamine (129.0 μL, 0.91 mmol, 1.1 eq). The resultant yellow mixture was stirred for 10 minutes before trifluoromethanesulfonic anhydride (153.0 μL, 0.91 mmol, 1.1 eq) was added. After 15 minutes triethylamine (127.0 μL, 0.91 mmol, 1.1 eq), followed by the trimethylsilyl trifluoromethanesulfonate (176.0 μL, 0.91 mmol, 1.1 eq), was added and the reaction mixture was stirred for 20 minutes.

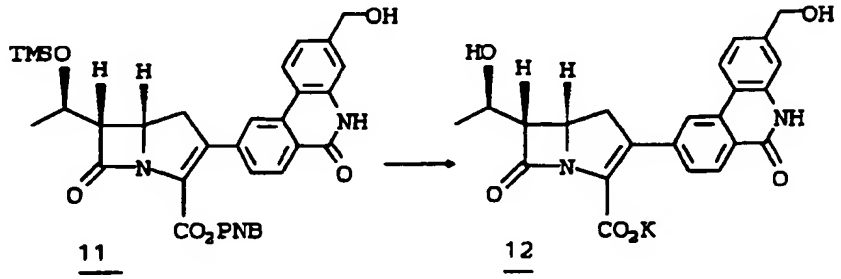
The reaction mixture was then treated sequentially with anhydrous N-methyl-2-pyrrolidinone (4.1 mL), the $Pd_2(dba)_3.CHCl_3$ catalyst (17.2 mg, 1.6 x 10^{-2} mmol, 2.0 mol%), tris (2,4,6-trimethoxyphenyl) phosphine (35.2 mg, 1.6 x 10^{-2} mmol, 8.0 mol%), the aryl-stannane 8 (214.0 mg, 0.55 mmol, 0.66 eq), and zinc chloride (0.55 mL, 0.55 mmol, 0.66 eq). The low temperature bath was then removed and the reaction vessel was placed in a warm water bath to quickly reach ambient temperature. The resulting wine-red solution was stirred for 40 minutes at ambient temperature.

The reaction was then poured into ether (250 mL) and washed with water (3x) and brine. The organic layer was dried ($MgSO_4$), decolorized briefly with Norite, filtered, and evaporated in vacuo. Purification using flash chromatography (100% EtOAc) provided 246 mg (71%) of the coupled product 10, a yellow foam.

^{1}H-NMR for 10 [400 MHz, $CDCl_3$]: δ 0.15 (s, 9H), 1.30 (d, J=6.0 Hz, 3H), 2.73 (broad t, J=5.7 Hz, 1H), 3.26 to 3.34 (complex m, 2H), 3.42 (½ ABX, J_{AB}=18.3 Hz, J_{AX}=8.7 Hz, 1H), 4.24 to 4.30 (m, 1H), 4.35 (dt, J=9.5, 2.7 Hz, 1H), 4.75 (d, J=5.8 Hz, 2H), 5.21 (ABq, J=13.3 Hz, $\Delta\upsilon_{AB}$=73.8 Hz, 2H), 7.04 (d, J=8.4 Hz, 1H), 7.26 (s, 1H), 7.31 (d, J=8.4 Hz, 2H), 7.44 (d, J=8.1 Hz, 1H), 7.74 (d, J=8.4 Hz, 1H), 7.91 (d, J=8.4 Hz, 2H), 8.04 (s, 1H), 8.43 (d, J=8.1 Hz, 1H), 10.85 (s, 1H).

IR ($CHCl_3$): 3400, 3010, 2980, 1780, 1725, 1665, 1610, 1520 cm^{-1}. U.V. (CH_3CN): λ= 315 nm, ε= 18,000.

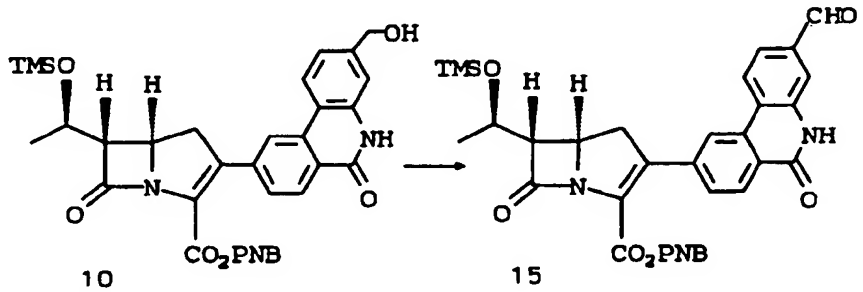
EXAMPLE 9



Acetic acid (6.3 μL, 0.11 mmol, 1.0 eq) was added to a stirred solution of 11 (68.8 mg, 0.11 mmol) in 1.3:1.3:1.0 THF/EtOH/H_2O, and the reaction mixture was stirred for 1.75 hours at 40°C. Potassium bicarbonate (23.1 mg, 0.23 mmol, 2.1 eq) was then added. The 10% Pd/C catalyst (6.9 mg, 10% wt) was added next, and the reaction mixture was hydrogenated under a H_2 balloon at ambient temperature for 1 hour. The mixture was then filtered through a pad of celite using water as the eluant, and the THF and EtOH solvent from the filtrate were removed in vacuo. The remaining water was then frozen and lyophilized at 0°C. Crude 12 was redissolved in a minimal amount of H_2O/CH_3CN and purified using Analtech reverse phase prep-plates (6:1 H_2O/CH_3CN) to provide 16.6 mg (36%) of carbapenem 12, a light-yellow solid.

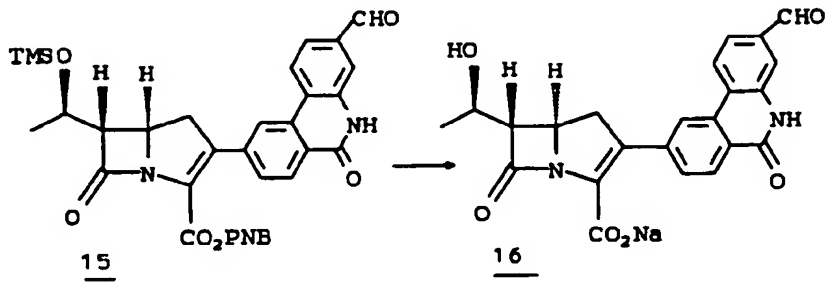
^{1}H-NMR for 12 [400 MHz, 2:1 D_2O/CD_3CN]: δ 1.69 (d, J=6.3 Hz, 3H), 3.56 (½ ABX, J_{AB}=16.6 Hz, J_{AX}=10.2 Hz, 1H), 3.87 to 3.95 (complex m, 2H), 4.59 to 4.64 (m, 1H), 4.73 (dt, J=9.3, 2.6 Hz, 1H), 5.07 (s, 2H), 7.65 (s,1H), 7.68 (d, J=8.7 Hz, 1H), 8.01 (d, J=8.1 Hz, 1H), 8.52 to 8.59 (m, 3H).
IR(KBr): 1755, 1660, 1615 cm^{-1}.
U.V.(MOPS Buffer): λ_{o1}=309 nm, ε_{o1} =16,000; λ_{o2}= 326nm, ε_{o2}=15,900; λ_{ext1}=309 nm, ε_{ext1}=10,600; λ_{ext2}=337 nm, ε_{ext2}=9,600; λ_{ext3}=349 nm, ε_{ext3}=8,300.

EXAMPLE 10



A stirred solution of 10 (121 mg, 0.19 mmol), N-methylmorpholine-N-oxide (33.8 mg, 0.29 mmol, 1.5 eq), and powdered 4Å molecular sieves (96 mg, 500 mg/mmol) in dry dichloromethane (1.9 mL) was treated with tetrapropylammoniumperruthenate (3.4 mg, 5.0 mol%) at room temperature under N_2. The reaction mixture was stirred for 10 minutes before the resulting black mixture was filtered through a short-column of silica gel using 75% EtOAc/hex as an eluant. The filtrate was evaporated in vacuo to afford 67 mg (56%) of aldehyde 15, a yellow oil.
^{1}H-NMR for 15 [400 MHz, $CDCl_3$]: δ 0.15 (s, 9H), 1.31 (d, J=6.2 Hz, 3H), 3.31 to 3.38 (complex m, 2H), 3.45 (½ ABX, J_{AB}=18.5 Hz, J_{AX}=8.9 Hz, 1H), 4.27 to 4.31 (m, 1H), 4.39(dt, J=9.5, 2.8 Hz, 1H), 5.25 (ABq, J=13.5 Hz, $\Delta\upsilon_{AB}$=68.7 Hz, 2H), 7.39 (d, J=8.7 Hz, 2H), 7.57 (d, J=8.3 Hz, 1H), 7.69 (d, J=8.3 Hz, 1H), 7.79 (s, 1H), 8.00 (d, J=8.7 Hz, 2H), 8.11 (d, J=8.3 Hz, 1H), 8.26 (s, 1H), 8.52 (d, J=8.2 Hz, 1H), 10.05 (s, 1H), 11.53 (s, 1H).
IR ($CHCl_3$): 3020, 2960, 1780, 1730, 1705, 1670, 1610, 1520 cm^{-1}.
U.V. (CH_3CN): λ=301 nm, ε=28,230.

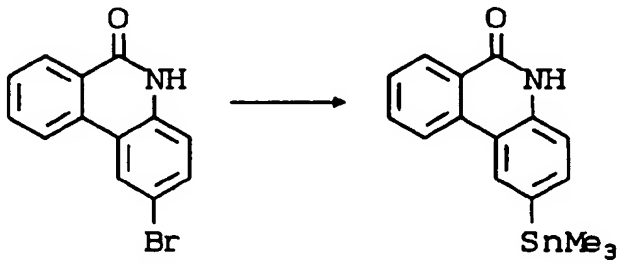
EXAMPLE 11



Anhydrous 1M HCl in ether (47.0 µL, 4.7 x 10^{-2} mmol, 0.50 eq) was added to a stirred solution of 15 (58.7 mg, 9.4 x 10^{-2} mmol) in 2:1 THF/H_2O at 0°C and the reaction mixture was stirred for 10 minutes at 0°C. Aqueous sodium bicarbonate solution (0.15 mL, 0.15 mmol, 1.6 eq) was then added and the ice bath was removed. After adding 10% Pd/C (5.8 mg, 10% wt) the reaction mixture was hydrogenated under a H_2 balloon at ambient temperature for 1 hour. The mixture was then filtered through a pad of celite using water as the eluant. The THF from the filtrate was removed in vacuo and the remaining water was frozen and lyophilized at 0°C. Crude 15 was redissolved in a minimal amount of H_2O/CH_3CN and purified using Analtech reverse phase prep-plates

eluted with 7:1 H_2O/CH_3CN. Carbapenem 16 was isolated as a yellowish solid in 37% yield (15.3 mg). ^{1}H-NMR for 16 [400 MHz, 2:1 D_2O/CD_3CN]: δ 1.71 (d, J=6.3 Hz, 3H), 3.59 (½ ABX, J_{AB}=16.5 Hz, J_{AX}=9.9 Hz, 1H), 3.90 to 3.96 (complex m, 2H), 4.62 to 4.66 (m, 1H), 4.75 (dt, J=9.7, 2.7 Hz, 1H), 8.13 (d, J=8.4 Hz, 1H), 8.19 (s, 1H), 8.21 (d, J=8.3 Hz, 1H), 8.64 (d, J=8.4 Hz, 1H), 8.71 (s, 1H), 8.78 (d, J=8.3 Hz, 1H), 10.39 (s, 1H).
IR (KBr): 3420, 1755, 1690, 1660, 1615 cm^{-1}. UV (MOPS Buffer): λ_0=305 nm, ε_0=19,600: λ_{ext1}=314 nm, ε_{ext1}=10,900; λ_{ext2}=367 nm, ε_{ext2}=4,970.

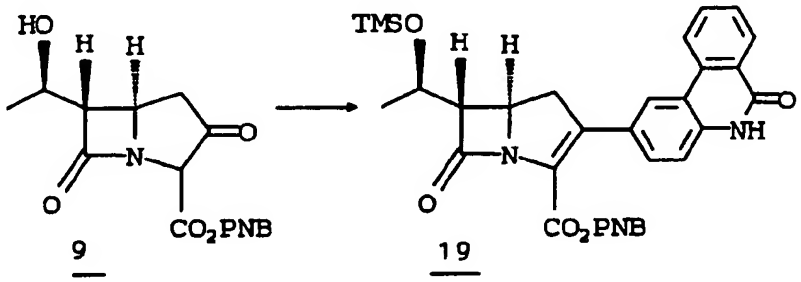
EXAMPLE 12



17 18

From 17 (0.5 g, 1.82 mmol), using the general stannylation procedure described for compound 8 was provided 498 mg (76%) of stannane 18, a white solid.
^{1}H-NMR for 18 [300 MHz, $CDCl_3$]: δ 0.36 (s, 9H), 7.41 (d, J=7.8 Hz, 1H), 7.57 to 7.64 (m, 2H), 7.80 (t, J=7.4 Hz, 1H), 8.31 (s, 1H) 8.33 (d, J=8.2 Hz, 1H), 8.59 (d, J=7.1 Hz, 1H), 11.23 (s, 1H).
IR ($CHCl_3$): 3400, 3010, 1665, 1610 cm^{-1}.

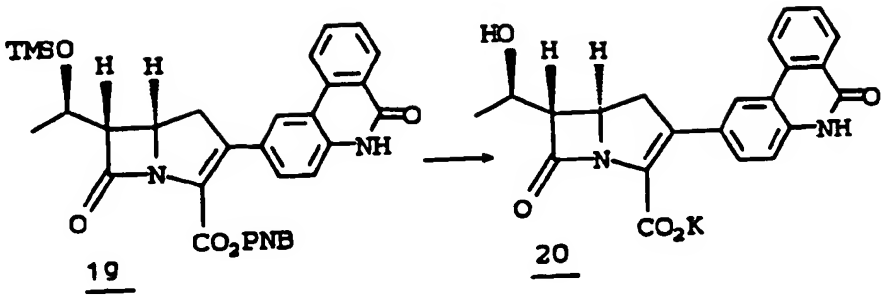
EXAMPLE 13



9 19

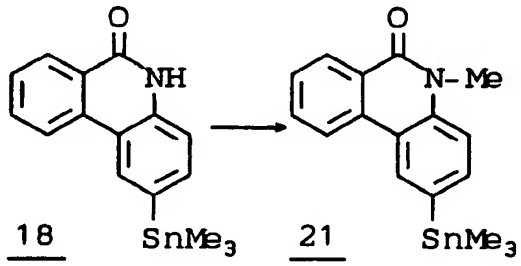
Following the general coupling procedure described for the synthesis of compound 10, the bicyclic β-keto ester 9 (160.5 mg, 0.46 mmol) was coupled to the aryl stannane 18 (150 mg, 0.42 mmol, 0.91 eq) to provide 169 mg (67%) of 19, a yellowish solid.
^{1}H-NMR for 19 [300 MHz, $CDCl_3$]: δ 0.15 (s, 9H), 1.31 (d, J=6.3 Hz, 3H), 3.27 to 3.38 (complex m, 3H), 4.25 to 4.34 (complex m, 2H), 5.28 (ABq, J=13.7 Hz, $\Delta\upsilon_{AB}$=53.3 Hz, 2H), 7.31 (d, J=8.4 Hz, 1H), 7.49 (m, 3H), 7.62 (t, J=7.1 Hz, 1H), 7.76 (t, J=7.1 Hz, 1H), 8.08 (d, J=8.7 Hz, 2H), 8.15 (d, J=8.2 Hz, 1H), 8.31 (s, 1H), 8.54 (d, J=7.6 Hz, 1H), 11.40 (s, 1H).
IR ($CHCl_3$): 3010, 2960, 1780, 1725, 1665, 1610, 1520 cm^{-1}.
UV (CH_3CN): λ=328 nm, ε=14,800.

EXAMPLE 14



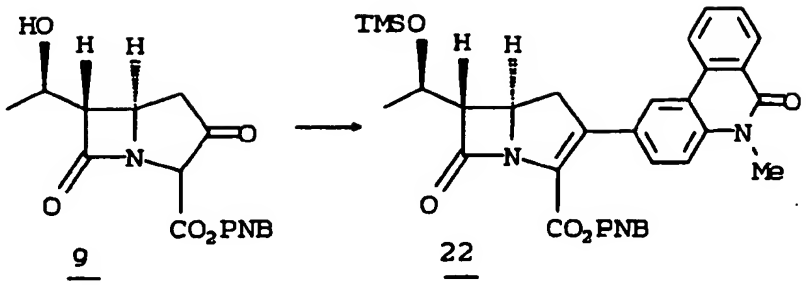
From 19 (169 mg, 0.28 mmol) in 1:1:1 THF/CH_3CN/H_2O, using the general deprotection procedure described for compound 12, was provided 83 mg (68%) of 20, a yellowish solid.
^{1}H-NMR for 20 [300 MHz, 2:1 D_2O/CD_3CN]: δ 1.68(d, J=6.4 Hz, 3H), 3.54 (½ ABX, J_{AB}=16.9 Hz, J_{AX}=9.8 Hz, 1H), 3.82 to 3.87 (complex m, 2H), 4.58 to 4.69 (complex m, 2H), 7.71 (d, J=8.5 Hz, 1H), 7.98 (d, J=8.5 Hz, 1H), 8.07 (t, J=7.2 Hz, 1H), 8.29 (t, J=7.2 Hz, 1H), 8.68 (s, 1H), 8.73 (d, J=8.1 Hz, 1H), 8.78 (d, J=8.2 Hz, 1H).
IR (KBr): 1755, 1670, 1630, 1605, 1550 cm^{-1} U.V. (MOPS Buffer): λ_0=323 nm, ε_0=17,000; λ_{ext1}=316 nm, ε_{ext1}=9,400; λ_{ext2}=331 nm, ε_{ext2}=7,900; λ_{ext3}=350 nm, ε_{ext3}=8,600.

EXAMPLE 15



To a suspension of sodium hydride (16.7 mg, 0.42 mmol, 1.0 eq, 60% in mineral oil) in anhydrous DMF (4.2 mL) and dry benzene (0.42 mL) was added 18 (150 mg, 0.42 mmol) at 0°C. After the evolution of H_2 gas had subsided the resultant yellow mixture was stirred at 100°C for 30 minutes. The reaction mixture was then cooled to 0°C and iodomethane (39.2 µL, 0.63 mmol, 1.5 eq) in anhydrous DMF (2.1 mL) was added. After stirring for 3.5 h at 100°C the resultant brown mixture was quenched with dropwise addition of saturated ammonium chloride solution (2 mL at 0°C. The reaction mixture was then poured into ethyl acetate (75 mL) and washed with water (1x), saturated sodium bicarbonate solution (1 x 25 mL), water (2x), and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification using flash chromatography (20% EtOAc/hex) provided 52.0 mg (33%) of stannane 21, a white solid.
^{1}H-NMR for 21 [300 MHz, $CDCl_3$]: δ 0.37 (s, 9H), 3.79 (s, 3H), 7.37 (d, J=8.1 Hz), 7.56 (t, J=7.1 Hz, 1H), 7.63 (d, J=8.2 Hz, 1H), 7.75 (t, J=7.2 Hz, 1H), 8.32 (d, J=7.9 Hz, 1H), 8.36 (s, 1H), 8.54 (d, J=7.7 Hz, 1H)
IR ($CHCl_3$): 3010, 2920, 1645, 1600, 1575 cm^{-1}.

EXAMPLE 16



9 22

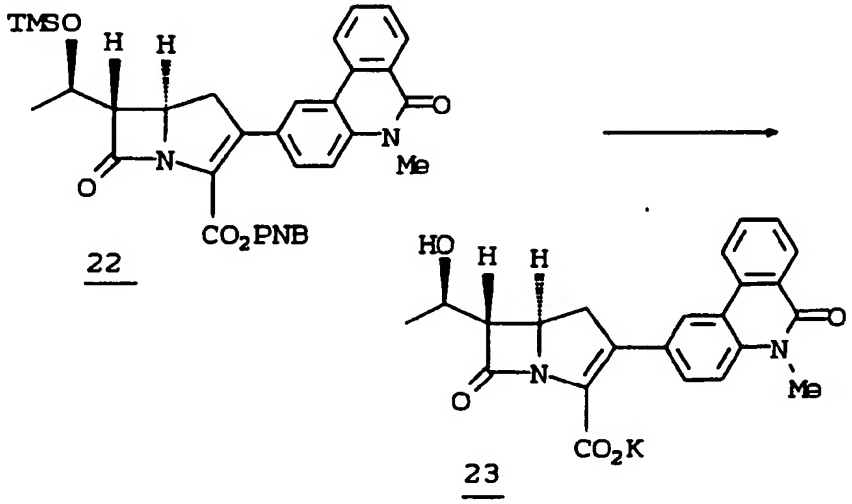
Following the general coupling procedure described for compound 10, the bicyclic β-keto ester 9 (58.4 mg, 0.167 mmol) was coupled to the aryl stannane 21 (52.0 mg, 0.14 mmol, 0.84 eq) to provide 56 mg (65%) of 22, a yellow oil.

^{1}H-NMR for 22 [300 MHz, $CDCl_3$]: δ 0.15 (s, 9H), 1.31 (d, J=6.3 Hz, 3H), 3.27 to 3.30 (m, 1H), 3.34 to 3.39 (complex m, 2H), 3.79 (s, 3H), 4.23 to 4.35 (complex m, 2H), 5.30 (ABq, J=13.7 Hz, $\Delta\upsilon_{AB}$=55.8 Hz, 2H), 7.36 (d, J=8.8 Hz, 1H), 7.52 to 7.60 (m, 4H), 7.72 (t, J=7.2 Hz, 1H), 8.10 (d, J=8.7 Hz, 2H), 8.14 (d, J=8.1 Hz, 1H), 8.38 (s, 1H), 8.52 (d, J=7.9 Hz, 1H).

IR ($CHCl_3$): 3020, 2970, 1775, 1725, 1650, 1610, 1520 cm^{-1}.

U.V.(CH_3CN):λ=333 nm, ε=11,700.

EXAMPLE 17



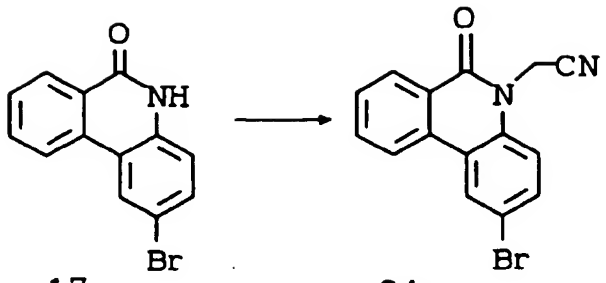
22 23

From 22 (56 mg, 0.092 mmol), using the general deprotection procedure described for compound 12, was provided 12.9 mg (32%) of carbapenem 23, a white solid.

^{1}H-NMR for 23 [300 MHz, D_2O]: δ 1.47(d, J=6.6 Hz, 3H), 3.18 to 3.26 (m, 1H), 3.46 to 3.64 (complex m, 2H), 3.53 (s, 3H), 4.39 to 4.49 (complex m, 2H), 7.27 (d, J=8.9 Hz, 1H), 7.52 (d, J=7.8 Hz, 1H), 7.59 (t, J=7.9 Hz, 1H), 7.74 (t, J=7.4 Hz, 1H), 7.88 (s, 1H), 7.95 (d, J=8.2 Hz, 1H), 8.12 (d, J=8.1 Hz, 1H). IR (KBr): 2980, 1740, 1640, 1605, 1575 cm^{-1}.

U.V. (MOPS Buffer): λ_o=320 nm, ε_o=12,000; λ_{ext1}=317 nm, ε_{ext1}=6,700; λ_{ext2}=352 nm, ε_{ext2}=5,100.

EXAMPLE 18

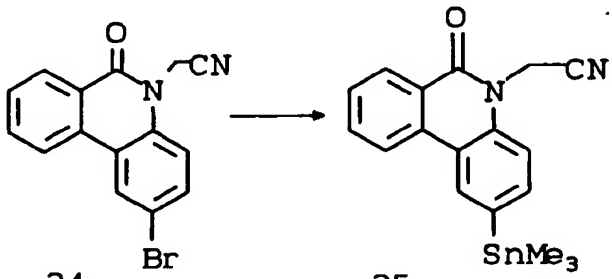


17 24

To a suspension of sodium hydride (73 mg, 1.82 mmol, 1.0 eq, 60% in mineral oil) in anhydrous DMF (18.2 mL) was added 17 (500 mg, 1.82 mmol) at 0°C. After the evolution of H_2 gas had subsided the resultant yellow mixture was stirred at 100°C for 30 minutes. The reaction mixture was then cooled to 0°C and bromoacetonitrile (0.14 mL, 2.0 mmol, 1.1 eq) in dry DMF (9.1 mL) was added. After stirring for 1 hour at 100°C the resultant black mixture was quenched with dropwise addition of saturated ammonium chloride solution (5 mL) at 0°C. The reaction mixture was then poured into ethyl acetate (175 mL) and washed with water (1x), saturated sodium bicarbonate solution (1 x 50 mL), water (2x), and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo. Recrystallization from ethyl acetate afforded 352 mg (62%) of the N-cyanomethyl compound 24, white crystalline needles.

^{1}H-NMR for 24 [300 MHz, D_6 DMSO]: δ 5.53 (s, 2H), 7.68 (d, J=9.2 Hz, 1H), 7.75 (t, J=7.7 Hz, 1H), 7.88 (d, J=8.9 Hz, 1H), 7.93 (t, J=8.1 Hz, 1H), 8.38 (d, J=7.8 Hz, 1H), 7.66 (d, J=8.5 Hz, 1H), 8.77 (s, 1H).
IR (KBr): 3000, 2960, 2250, 1660, 1605 cm^{-1}.

EXAMPLE 19

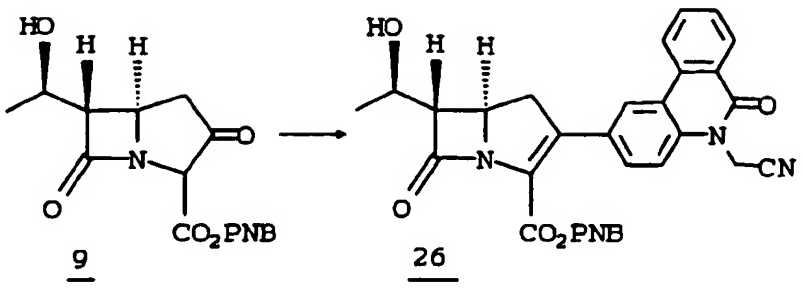


24 25

From 24 (382 mg, 0.48 mmol), using the general stannylation procedure described for compound 8, was provided 379 mg (78%) of stannane 25, a white solid.

^{1}H-NMR for 25 [300 MHz, $CDCl_3$]: δ 0.38 (s, 9H), 5.33 (s, 2H), 7.35 (d, J=8.2 Hz, 1H), 7.57 (t, J=8.2 Hz, 1H), 7.70 (d, J=8.2 Hz, 1H), 7.80 (t, J=8.4 Hz, 1H), 8.31 (d, J=7.8 Hz, 1H), 8.38 (s, 1H), 8.49 (d, J=6.9 Hz, 1H).
IR ($CHCl_3$): 3010, 2990, 2980, 2920, 2260, 1660, 1615, 1601, 1580 cm^{-1}.

EXAMPLE 20



9 26

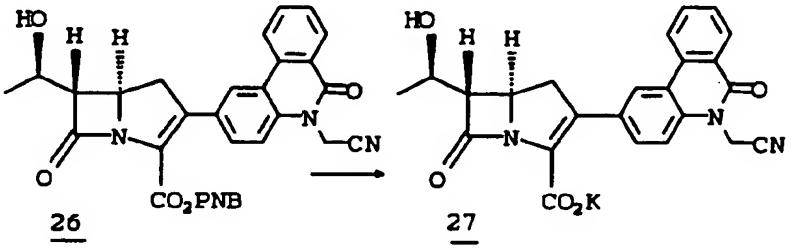
To a stirred solution of the bicyclic β-keto ester 9 (376.0 mg, 1.08 mmol) in dry THF (5.4 mL) at -78°C under N_2 was added diisopropylamine (0.17 mL, 1.19 mmol, 1.1 eq). The resultant yellow mixture was stirred for 10 minutes before trifluoromethane sulfonic anhydride (0.20 mL, 1.19 mmol, 1.1 eq) was added. After 15 minutes the reaction mixture was treated sequentially with anhydrous N-methyl-2-pyrrolidinone (5.4 mL), the $Pd_2(dba)_3 \cdot CHCl_3$ catalyst (22.4 mg, 2.2×10^{-2} mmol, 2.0 mol%), tris (2,4,6-trimethoxyphenyl)phosphine (46.0 mg, 8.6×10^{-2} mmol, 8.0 mol%) the aryl stannane 25 (357.2 mg, 0.90 mmol, 0.83 eq), and zinc chloride (0.6 mL, 0.90 mmol, 0.83 eq). The low temperature bath was then removed and the reaction vessel was placed in a warm water bath to quickly reach ambient temperature. The resulting wine-red solution was stirred for 40 minutes at ambient temperature.

The reaction was then poured into ether (250 mL) and washed with water (3x) and brine. The organic layer was dried ($MgSO_4$), decolorized briefly with Norite, filtered, and evaporated in vacuo. Purification using flash chromatography (80%) EtOAc/hex) provided 201.9 mg (71%) of the coupled product 26, a yellow solid.

^{1}H-NMR for 26 [300 MHz, $CDCl_3$]: δ 1.40 (d, J=6.3 Hz, 3H), 3.29 to 3.46 (complex m, 3H), 4.28 to 4.42 (complex m, 2H), 5.29 (ABq, J=13.4 Hz, $\Delta \upsilon_{AB}$ = 59.3 Hz, 2H), 5.33 (s, 2H), 7.34 (d, J=8.7 Hz, 1H), 7.49 (d, J=8.5 Hz, 2H), 7.57 to 7.63 (m, 2H), 7.76 (t, J=7.6 Hz, 1H), 8.07 (d, J=8.6 Hz, 2H), 8.12 (d, J=8.2 Hz, 1H), 8.39 (s, 1H), 8.45 (d, J=8.0 Hz, 1H).

IR ($CHCl_3$): 3600, 3200, 2980, 1780, 1730, 1665, 1605, 1520 cm^{-1}. U.V. (CH_3CN): λ=325 nm, ε=10,000.

EXAMPLE 21



26 27

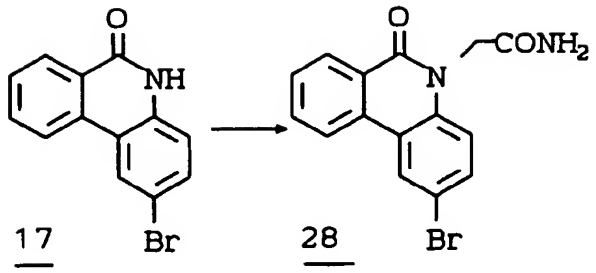
To a stirred solution of 26 (201 mg, 0.356 mmol) and potassium bicarbonate (39.2 mg, 0.392 mmol, 1.1 eq) in 2:1 acetone/H_2O was added 10% Pd/C catalyst (20.1 mg, 10% wt), and the reaction mixture was hydrogenated under an H_2 balloon at ambient temperature for 1.6 hours. The mixture was then filtered through a pad of celite using water as the eluant, and the acetone solvent from the filtrate was removed in vacuo. The remaining water was then frozen and lyophilized at 0°C. Crude 27 was redissolved in a minimal amount of H_2O/CH_3CN and purified using Analtech reverse phase prep-plates (3:1 H_2O/CH_3CN) to provide 43.6 mg (26%) of 27, a white solid.

^{1}H-NMR for 27 [300 MHz, 2:1 D_2O/CD_3CN]: δ 1.51 (d, J=6.3 Hz, 3H), 3.36 (½ ABX, J_{AB}=15.6 Hz, J_{AX}=8.9 Hz, 1H), 3.63 to 3.71 (complex m, 2H), 4.43 to 4.57 (complex m, 2H), 5.54 (s, 2H), 7.66 (d, J=9.3 Hz, 1H), 7.67 to 7.83 (m, 2H), 8.01 (t, J=8.8 Hz, 1H), 8.17 to 8.44 (m, 3H).

IR (KBr): 2980, 1755, 1650, 1601, 1570 cm^{-1}.

UV (MOPS Buffer): λ_o=316 nm, ε_o=13,600; λ_{ext1}=312 nm, ε_{ext1}=8,100; λ_{ext2}=349 nm, ε_{ext2}=5,800.

EXAMPLE 22

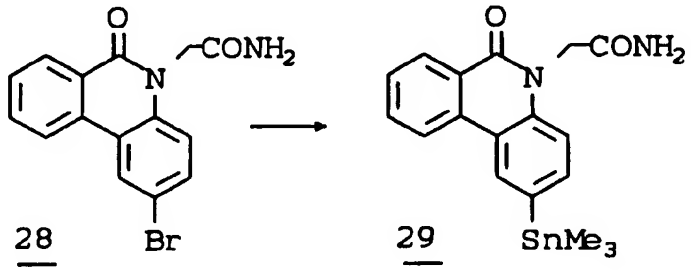


From 17 (350 mg, 1.28 mmol) and iodoacetamide (362 mg, 1.92 mmol, 1.5 eq) as the alkylating agent, using the general procedure described for compound 24 was provided 357 mg (84%) of the N-acetamide 28, a white solid.

^{1}H-NMR for 28 [300 MHz, D_6 DMSO]: δ 4.97 (s, 2H), 7.26 (d, J=9.2 Hz, 1H), 7.31 (s, 1H), 7.68 to 7.75 (m, 3H), 7.88 (t, J=7.2 Hz, 1H), 8.36 (d, J=7.8 Hz, 1H), 8.62 (d, J=8.1 Hz, 1H), 8.69 (s, 1H).

IR (KBr): 3200, 1685, 1650, 1610 cm^{-1}.

EXAMPLE 23

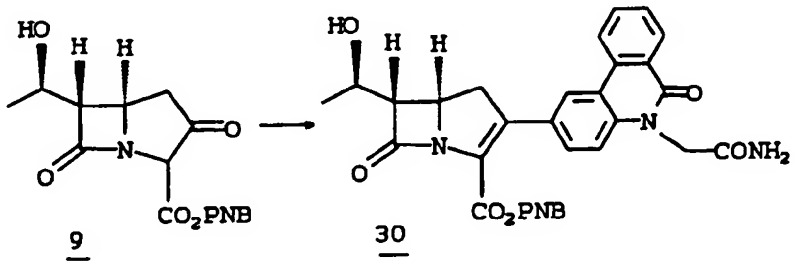


From 28 (280.7 mg, 0.85 mmol) in anhydrous DMF (8.5 mL), using the general stannylation procedure described for compound 8, was provided 69 mg (19%) of stannane 29, a yellowish solid.

^{1}H-NMR for 29 [300 MHz, $CDCl_3$]: δ 0.36 (s, 9H), 5.02 (s, 2H), 5.39 (broad s, 1H), 6.31 (broad s, 1H), 7.52 (d, J=8.2 Hz, 1H), 7.60 (t, J=7.6 Hz, 1H), 7.65 (d, J=8.2 Hz, 1H), 7.80 (t, J=8.0 Hz, 1H), 8.35 (d, J=8.2 Hz, 1H), 8.39 (s, 1H), 8.52 (d, J=8.2 Hz, 1H).

IR ($CHCl_3$): 3490, 3410, 3010, 2915, 1690, 1640, 1605, 1570 cm^{-1}.

EXAMPLE 24

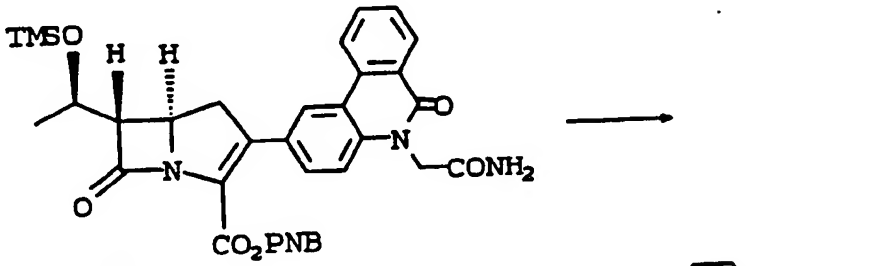


Following the general coupling procedure described for compound 10, the bicyclic β-keto ester 9 (54.0 mg, 0.15 mmol) was coupled to the aryl stannane 29 (45.5 mg, 0.13 mmol, 0.83 eq) to provide 11.7 mg (14%) of the coupled product 30, a yellowish solid.

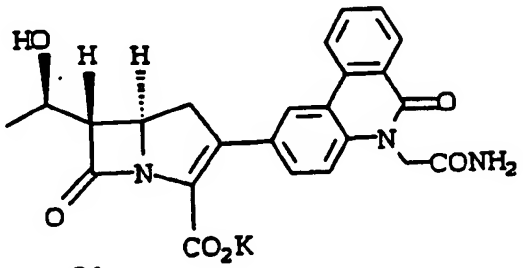
^{1}H-NMR for 30 [300 MHz, $CDCl_3$]: δ 0.15 (s, 9H), 1.31 (d, J=6.0 Hz, 3H), 3.25 to 3.36 (complex m, 3H), 4.22

to 4.34 (complex m, 2H), 4.99 (s, 2H), 5.28 (ABq, J=13.7 Hz, $\Delta \upsilon_{AB}$=53.3 Hz, 2H), 5.48 (broad s, 1H), 6.42 (broad s, 1H), 7.46 (d, J=8.7 Hz, 2H), 7.53 (s, 2H), 7.60 (t, J=7.5 Hz, 1H), 7.76 (t, J=7.4 Hz, 1H), 8.05 (d, J=8.2 Hz, 2H), 8.14 (d, J=8.5 Hz, 1H), 8.39 (s, 1H), 8.49 (d, J=7.8 Hz, 1H).
IR ($CHCl_3$): 3490, 3410, 3200, 2860, 1775, 1720, 1695, 1650, 1610, 1575, 1520 cm^{-1}.
U.V. (CH_3CN): λ_1=258 nm, ε_1=25,400; λ_2=324, ε_2=14,200.

EXAMPLE 25



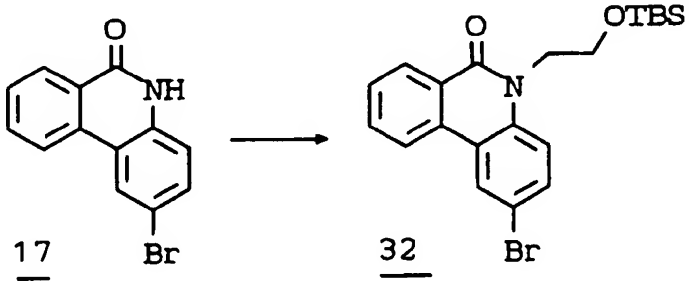
30



31

From 30 (11.1 mg, 0.017 mmol), using the general deprotection procedure described for compound 12, was provided 4.0 mg (49%) of carbapenem 31, a white solid.
^{1}H-NMR for 31 [300 MHz, 4:1 D_2O/CD_3CN]: δ 1.50 (d, J=6.3 Hz, 3H), 3.34 (½ ABX, J_{AB} = 16.2 Hz, J_{AX} = 8.4 Hz, 1H), 3.68 to 3.71 (complex m, 2H), 4.42 to 4.56 (complex m, 2H), 5.20 (s, 2H), 7.42 (d, J=8.5 Hz, 1H), 7.73 (d, J=8.4 Hz, 1H), 7.81 (t, J=8.4 Hz, 1H), 8.02 (t, J=8.4 Hz, 1H), 8.42 to 8.45 (m, 3H).
IR (KBr): 2980, 1750, 1680, 1640 1610, 1575 cm^{-1}. U.V. (MOPS Buffer): λ_o=318nm, ε_o=12,000; λ_{ext1}=280nm, ε_{ext1}=6,900; λ_{ext2}=315nm, ε_{ext2}=7,500; λ_{ext3}=350nm, ε_{ext3}=5,700.

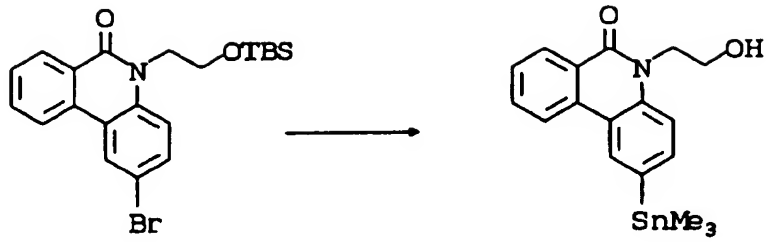
EXAMPLE 26



17 32

From 17 (2.0 g, 7.3 mmol) and 2-bromo(t-butyldimethylsilyl) ethanol (1.57 mL, 8.7 mmol, 1.2 eq) using the general alkylating procedure described for compound 24, was provided 2.1 g (69%) of bromide 32, a white crystalline solid.
^{1}H-NMR for 32 [300 MHz, $CDCl_3$]: δ 0.10 (s, 9H), 0.80 (s, 6H), 4.00 (t, J=6.0 Hz, 2H), 4.47 (t, J=6.0 Hz, 2H), 7.55 to 7.61 (m, 3H), 7.75 (t, J=8.4 Hz, 1H), 8.17 (d, J=7.7 Hz, 1H), 8.32 (s, 1H), 8.51 (d, J=7.9 Hz, 1H).
IR ($CHCl_3$): 3010, 2980, 2930, 2860, 1645, 1605, 1580 cm^{-1}.

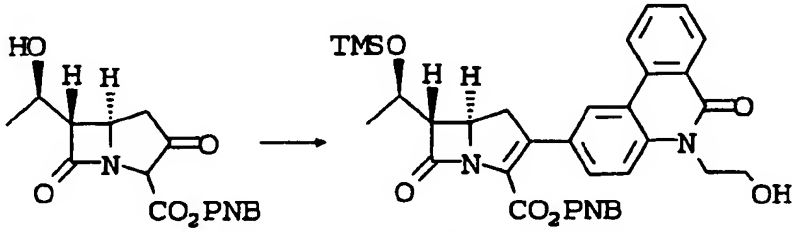
EXAMPLE 27



32 33

The bromide 32 (2.14 g, 5.1 mmol) was stannylated following the general stannylation procedure described for compound 8. The crude TBS-protected stannane was then redissolved in dry THF (51 mL), and tetrabutylammonium fluoride (7.6 mL, 7.6 mmol, 1.5 eq) was added at 0°C. The reaction mixture was then stirred for 1h at room temperature, poured into ethyl acetate, and washed with water (1x), saturated ammonium chloride solution (1x), water (2x), and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification using flash chromatography (40% EtOAc/hex) provided 1.34 g (65%) of stannane 33, a white solid.
^{1}H-NMR for 33 [300 MHz, $CDCl_3$]:δ 0.36 (s, 9H), 2.86 (t, J=5.2 Hz, 1H), 4.07 to 4.12 (m, 2H), 4.62 (t, J=5.5 Hz, 2H), 7.43 (d, J=8.2 Hz, 1H), 7.56 to 7.64 (m, 2H), 7.78 (t, J=7.4 Hz, 1H), 8.34 (d, J=8.2 Hz, 1H), 8.40 (s, 1H), 8.51 (d, J=8.2 Hz, 1H).
IR ($CHCl_3$): 3540 to 3320, 3020, 1630, 1607, 1570cm^{-1}.

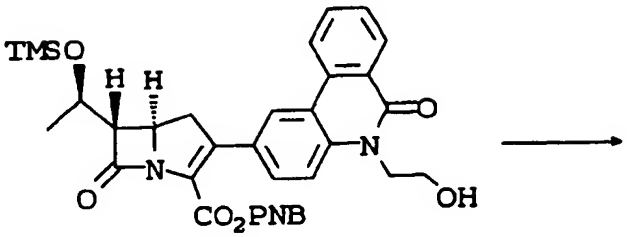
EXAMPLE 28



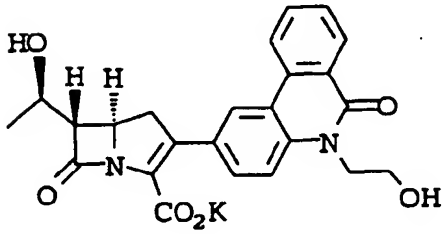
9 34

Following the general coupling procedure described for compound 10, the bicyclic β-keto ester 9 (506 mg, 1.45 mmol) was coupled to the aryl stannane 33 (509 mg, 1.21 mmol, 0.83 eq) to provide 621 mg (80%) of 34, a yellow foam.
^{1}H-NMR for 34 [300 MHz, $CDCl_3$]: δ 0.15 (s, 9H), 1.30 (d, J=6.0 Hz, 3H), 2.86 (broad t, J=4,8 Hz, 1H), 3.27 to 3.37 (complex m, 3H), 4.06 (d, J=4.9 Hz, 2H), 4.23 to 4.34 (complex m, 2H), 4.58 (t, J=5.2 Hz, 2H), 5.29 (ABq, J=13.7 Hz, $\Delta\upsilon_{AB}$=53.7 Hz, 2H), 7.42 to 7.59 (m, 5H), 7.70 (t, J=7.6 Hz, 1H), 8.08 (d, J=8.4 Hz, 2H), 8.12 (d, J=8.1 Hz, 1H), 8.39 (s, 1H), 8.46 (d, J=7.8 Hz, 1H).
IR ($CHCl_3$): 3600 to 3240, 3010, 2960, 1775, 1720, 1640, 1610, 1520 cm^{-1}.
U.V. (CH_3CN): λ=330 nm, ε=11,300.

EXAMPLE 29



34



35

From 34 (18.9 mg, $2.9x10^{-2}$ mmol), using the general deprotection procedure described for compound 12, was provided 5.4 mg (39%) of carbapenem 35, a yellow solid.

^{1}H-NMR for 35 [300 mHz, D_2O]: δ 1.47 (d, J=6.3 Hz, 3H), 3.34 (½ ABX, J_{AB}=16.3 Hz, J_{AX} = 9.3 Hz, 1H), 3.64 to 3.97 (complex m, 2H), 4.41 (broad t, J=5.7 Hz, 2H), 4.39 to 4.56 (complex m, 4H), 7.48 (d, J=8.8 Hz, 1H), 7.58 (d, J= 8.2 Hz, 1H), 7.67 (t, J=7.4 Hz, 1H), 7.86 (t, J=7.3 Hz, 1H), 8.11 to 8.16 (m, 2H), 8.26 (d, J=8.2 Hz, 1H).

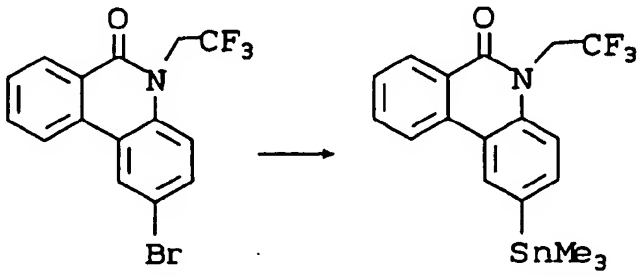
IR (KBr): 2980, 2920, 1750, 1640, 1610, 1580cm^{-1}. UV (MOPS Buffer): λ_o=324 nm, ε_o=8,680: λ_{ext1}=318 nm, ε_{ext1}=5,110; λ_{ext2}=351 nm, ε_{ext2}=4,090.

From 17 (500 mg, 1.82 mmol) and 2-bromo-1,1,1-trifluoroethane (1.9 mL, 20.9 mmol, 11.5 eq) using the general alkylating procedure described for compound 24, was provided 189 mg (29%) of bromide 38, a white solid.

^{1}H-NMR for 38 [300 MHz, $CDCl_3$]: δ 5.05 (broad d, J= 7.4 Hz, 2H), 7.26 (d, J=8.3 Hz, 1H), 7.59 to 7.64 (m, 2H), 7.73 (t, J=7.7 Hz, 1H), 8.16 (d, J=8.2 Hz, 1H), 8.34 (s, 1H), 8.50 (d, J=7.2 Hz, 1H).

IR ($CHCl_3$): 3200, 1670, 1610, 1580, 1560 cm^{-1}.

EXAMPLE 31



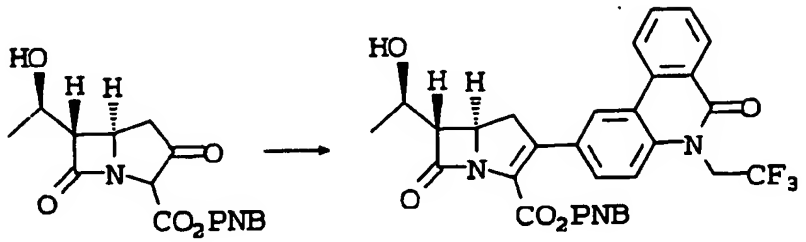
38 39

From 38 (189 mg, 0.53 mmol), using the general stannylaton procedure described for compound 8, was provided 171 mg (73 %) of stannane 39, a white crystalline solid.

^{1}H-NMR for 39 [300 MHz, $CDCl_3$]: δ 0.28 (s, 9H), 5.09 (broad d, J=7.8 Hz, 2H), 7.38 (d, J=8.2 Hz, 1H), 7.57 (d,

J=7.1 Hz, 1H), 7.62 (t, J=7.7 Hz, 1H), 7.79 (t, J=7.0 Hz, 1H), 8.32 (d, J=8.2 Hz, 1H), 8.38 (s, 1H), 8.53 (d, J = 6.8 Hz, 1H).
IR ($CHCl_3$): 3010, 2980, 2910, 1660, 1605, 1590, 1575 cm^{-1}.

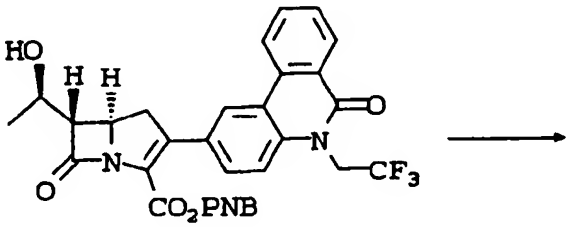
EXAMPLE 32



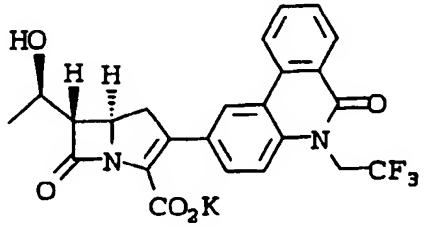
9 40

Following the coupling procedure described for compound 26, the bicyclic β-keto ester 9 (80 mg, 0.23 mmol) was coupled to the aryl stannane 39 (91.9 mg, 0.21 mmol, 0.91 eq) to provide 86.7 mg (68%) of carbapenem 40, a yellow solid.
^{1}H-NMR for 40 [300 MHz, $CDCl_3$]: δ 1.39 (d, J=6.3 Hz, 3H), 3.32 to 3.43 (complex m, 3H), 4.28 to 4.41 (complex m, 2H), 5.07 (broad d, J=7.7 Hz, 2H), 5.29 (ABq, J=13.5 Hz, $\Delta\upsilon_{AB}$ = 59.5 Hz, 2H), 7.35 (d, J=8.8 Hz, 1H), 7.47 to 7.52 (m, 3H), 7.58 (t, J=7.8 Hz, 1H), 7.73 (t, J=7.7 Hz, 1H), 8.06 (d, J=8.8 Hz, 2H), 8.11 (d, J=8.2 Hz, 1H), 8.38 (s, 1H), 8.49 (d, J=6.7 Hz, 1H).
IR ($CHCl_3$): 3010, 2970, 1775, 1720, 1670, 1610, 1520 cm^{-1}.
U.V. (CH_3CN): λ=324 nm, ε=14,600.

EXAMPLE 33



40

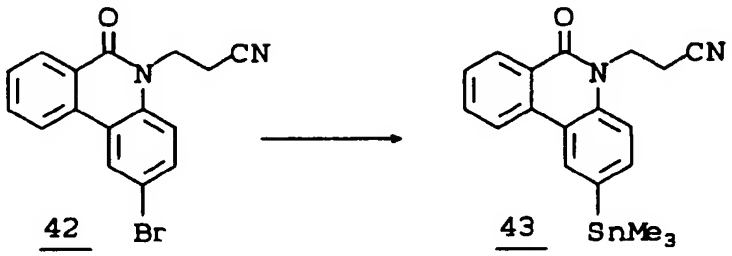


41

From 40 (54.7 mg, 0.09 mmol), using the deprotection procedure described for compound 27, was provided 30.4 mg (66%) of carbapenem 41, a white solid.
^{1}H-NMR for 41 [300 MHz, 2:1 D_2O/CD_3CN]: δ 1.73 (d, J=6.0 Hz, 3H), 3.62 (½ ABX, J_{AB}=16.2 Hz, J_{AX}=10.0 Hz, 1H), 3.87 to 3.93 (complex m, 2H), 4.64 to 4.75 (complex m, 2H), 5.69 (broad d, J=8.7 Hz, 2H), 8.05 to 8.19 (m, 3H), 8.39 (t, J=7.7 Hz, 1H), 8.85 to 8.95 (m, 3H).

IR (KBr): 2980, 1750, 1660, 1650, 1605, 1580 cm^{-1}. U.V. (MOPS Buffer): λ_o=322 nm, ε_o=12,000, λ_{ext1}=315 nm, ε_{ext1}=6,300, λ_{ext2}=348 nm, ε_{ext2}=4,500.

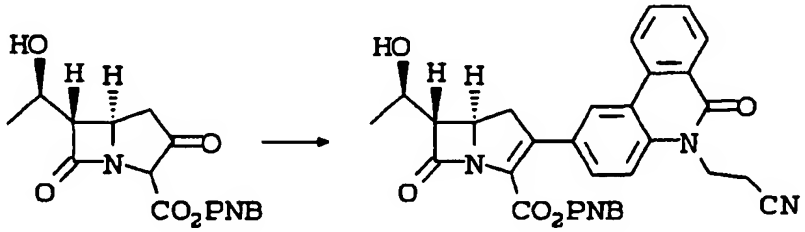
EXAMPLE 34



42 43

From 42 (54.7 mg, 0.17 mmol), using the general stannylation procedure described for compound 8, was provided 34.5 mg (50%) of stannane 43, a white foam.
^{1}H-NMR for 43 [300 MHz, $CDCl_3$]: δ 0.37 (s, 9H), 2.88 (t, J=7.4 Hz, 2H), 4.68 (t, J=7.4 Hz, 2H), 7.38 (d, J=8.2 Hz, 1H), 7.58 (t, J=7.7 Hz, 1H), 7.67 (d, J=8.2 Hz, 1H), 7.78 (t, J=7.7 Hz, 1H), 8.33 (d, J=8.2 Hz, 1H), 8.40 (s, 1H), 8.50 (d, J=8.1 Hz, 1H).
IR ($CHCl_3$): 3010, 2920, 2260, 1640, 1610, 1580 cm^{-1}.

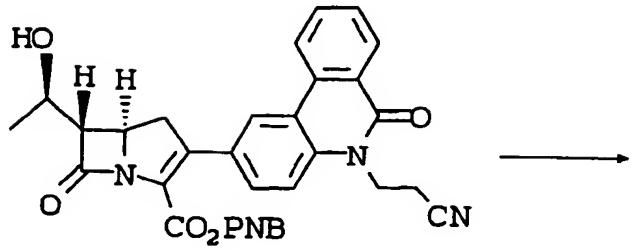
EXAMPLE 35



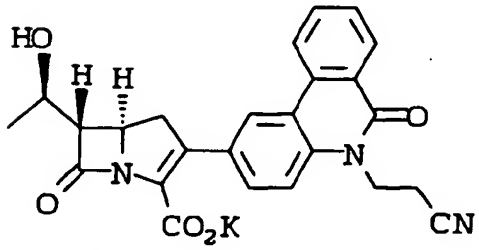
9 44

Following the coupling procedure described for compound 26, the bicyclic β-keto ester 9 (50.1 mg, 0.14 mmol) was coupled to the aryl stannane 43 (53.8 mg, 0.13 mmol, 0.91 eq) to provide 25.3 mg (33%) of 44, a white solid.
^{1}H-NMR for 44 [300 MHz, D_6 DMSO, Poorly resolved]: δ 1.19 (d, J=6.3 Hz, 3H), 2.98 to 3.07 (broad s, 2H), 3.45 to 3.49 (complex m, 2H), 3.62 to 3.74 (m, 1H), 3.98 to 4.07 (m, 1H), 4.25 to 4.36 (m, 1H), 4.60 to 4.70 (broad s, 2H), 5.15 to 5.38, (m, 2H), 7.43 to 7.46 (m, 2H), 7.62 to 7.73 (m, 3H), 7.80 to 7.83 (broad s, 1H), 7.96 to 8.02 (m, 2H), 8.31 to 8.35 (m, 1H), 8.42 to 8.46 (m, 1H), 8.53 (s, 1H).
IR (KBr): 3110, 3060, 2960, 2250, 1780, 1715, 1630, 1605, 1575, 1515cm^{-1}.

EXAMPLE 36



44

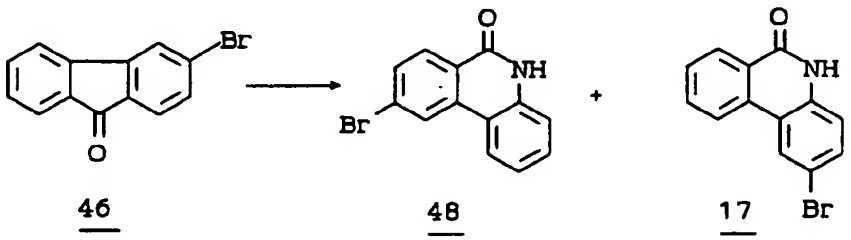


45

From 44 (17.8 mg, $3.1x10^{-2}$ mmol), using the deprotection procedure described for compound 27, was provided 8.5 mg (57%) of carbapenem 45, a white solid ^{1}H-NMR for 45 [300 MHz, 2:1 D_2O/CD_3CN]: δ 1.74 (d, J=6.4 Hz, 3H), 3.47 (t, J=6.3 Hz, 2H), 3.63 (½ ABX, J_{AB} = 16.7 Hz, J_{AX} = 9.8 Hz, 1H), 3.87 to 4.00 (complex m, 2H), 4.64 to 4.78 (complex m, 2H), 5.16 (t, J=6.8 Hz, 2H), 8.04 (d, J=8.9 Hz, 1H), 8.12 to 8.17 (m, 2H), 8.37 (t, J=7.7 Hz, 1H), 8.84 to 8.92 (m, 3H).
IR (KBr): 2970, 2920, 2250, 1750, 1640, 1610, 1585 cm^{-1}.
U.V. (MOPS Buffer): λ_o=319 nm, ε_o=15,400; λ_{ext1}=316 nm, ε_{ext1}=9,200; λ_{ext2}=350 nm, ε_{ext2}=6,600.

EXAMPLE 37

Method A:

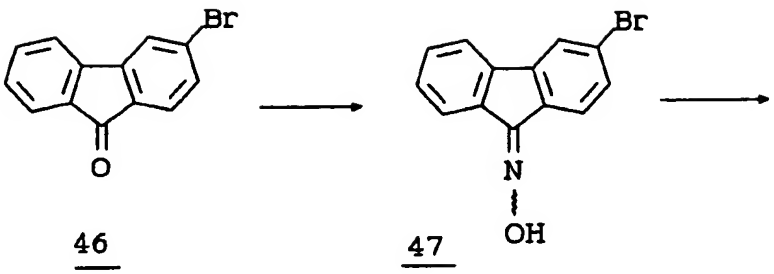


46 48 17

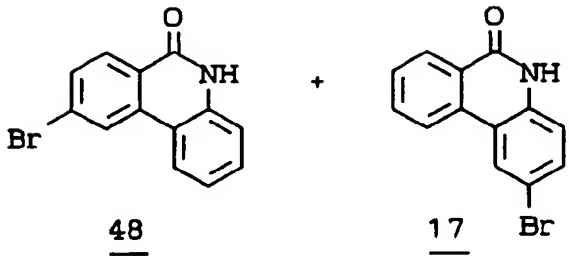
To a stirred solution of 46 (200 mg, 0.77 mmol) in concentrated sulfuric acid (12.9 mL) at 0°C was added a solution of sodium azide (75.3 mg, 1.16 mmol, 1.5 eq) in water (1 mL). After stirring the resultant black mixture for 24 hours at room temperature, ice-water (10 mL) was added. The reaction mixture was then stirred for 15 minutes, poured into ethyl acetate (200 mL), and washed with saturated sodium bicarbonate solution (2 x 25 mL), water (2x), and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo to obtain a mixture of 1:1 inseparable bromo-phenanthridone isomers (48 and 17) in 74% yield (156 mg).

EXAMPLE 38

Method B:



46 47



48 17

A suspension of 46 (200 mg, 0.77 mmol) and hydroxylamine hydrochloride (161 mg, 2.32 mmol, 3.0 eq) in anhydrous pyridine (7.7 mL) was sonicated to afford dissolution. The homogeneous mixture was then stirred at room temperature for 3.5 hour and poured into ether (100 mL). The ethereal layer was washed with water (1x), 1N HCl solution (4 x 15 mL), saturated sodium bicarbonate solution (2 x 15 mL), water (2x), and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo to afford 200 mg (95%) of the hydroxylamine isomers 47, a white solid. [The hydroxylamine isomers 47 was not characterized and was taken to the next step].

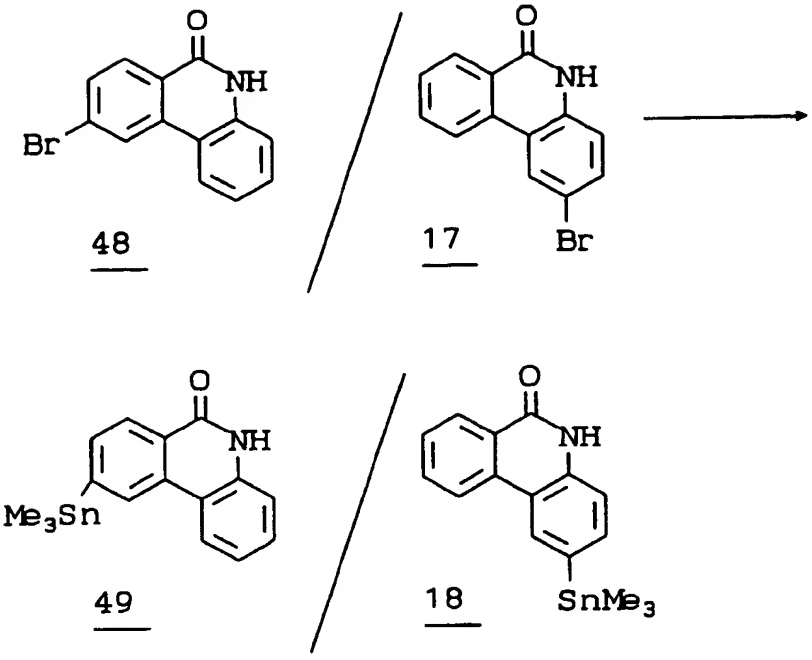
A mixture of 47 (104 mg, 0.38 mmol) in an excess amount of polyphosphoric acid (9g) was heated to 200°C. After 30 minutes the resultant black paste was dissolved in ice-water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were then washed with saturated sodium bicarbonate solution (3 x 25 mL), water (2x), and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo. The inseparable 1:1 mixture of the phenanthridone isomers (48 and 17) was isolated in 96% yield (100 mg) as a beige solid.

^{1}H-NMR for 48/17 [300 MHz, D_6 DMSO, mixture]: δ 7.24 to 7.38 (m, 3H), 7.52 (t, J=6.9 Hz, 1H), 7.64 to 7.71 (m, 2H), 7.79 to 7.89 (m, 2H), 8.22 (d, J=8.5 Hz, 1H), 8.32 (d, J=7.4 Hz, 1H), 8.45 (d, J=7.8 Hz, 1H), 8.56 to 8.60 (m, 2H), 8.75 (s, 1H).

IR (KBr): 3020, 2880, 1685, 1610 cm^{-1}.

Fast atom bombardment mass spectrum: m/e 274, 276 (calculated MH+ for $C_{13}H_8BrNO$= 274, 276).

EXAMPLE 39

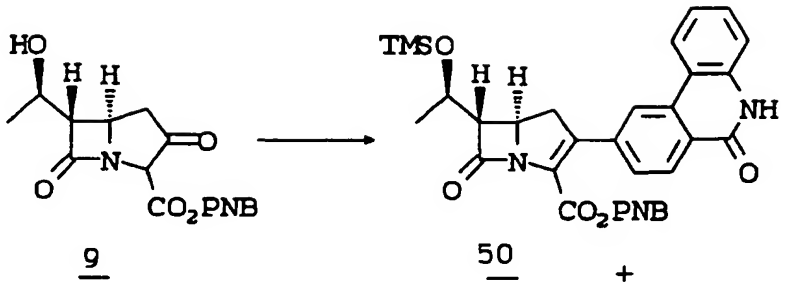


From an inseparable mixture of compounds 48 and 17 (125 mg, 0.46 mmol), using the general stannylation procedure described for compound 8, was provided 136 mg (83%) of an inseparable 1:1 mixture of stannanes 49 and 18, a white foam.

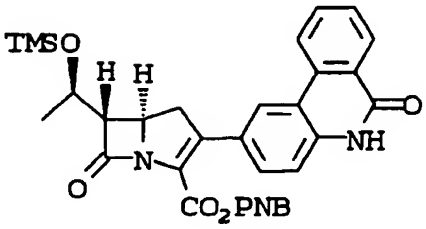
^{1}H-NMR for 49/18 [400 MHz, $CDCl_3$, mixture]: δ 0.36 (s, 9H), 0.40 (s, 9H), 7.29 to 7.32 (m, 3H), 7.47 (t, J=7.7 Hz, 1H), 7.56 to 7.62 (m, 2H), 7.74 (d, J=8.5 Hz, 1H), 7.80 (t, J=7.7 Hz, 1H), 8.33 (d, J=8.3 Hz, 1H), 8.31 (s, 1H), 8.35 (d, J=8.8 Hz, 1H), 8.42 (s, 1H), 8.48 (d, J=7.7 Hz, 1H), 8.55 (d, J=8.2 Hz, 1H), 10.12 (broad s, 1H), 10.23 (broad s, 1H).

IR ($CHCl_3$, mixture): 3270, 3010, 2915, 1660, 1601, 1555 cm^{-1}.

EXAMPLE 40



9 50 +



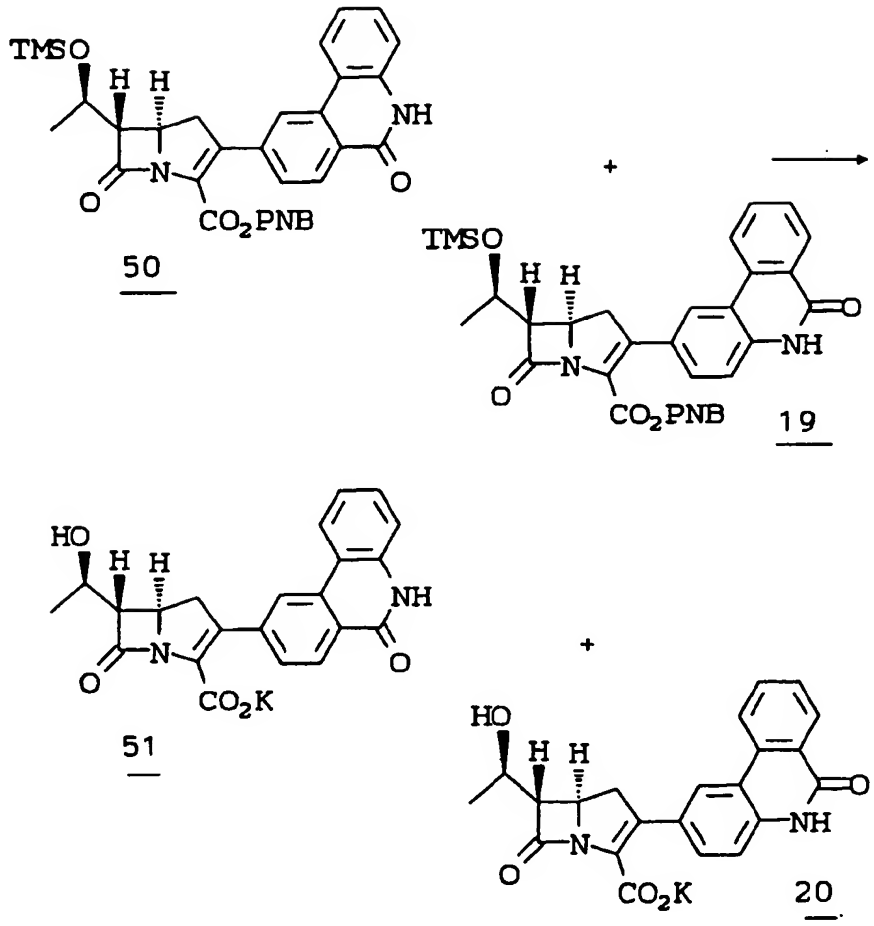
19

Following the general coupling procedure described for the synthesis of compound 10, the bicyclic β-keto ester 9 (162.4 mg, 0.47 mmol, 1.1 eq) was coupled to a mixture of the aryl stannanes 49 and 18 (152 mg, 0.42 mmol, 1.1 eq), to provide 172 mg (68%) of a 1.2:1.0 inseparable mixture of compounds 50 and 19, respectively, as a yellow foam.

^{1}H-NMR for 50/19 [300 MHz, $CDCl_3$, mixture]: δ 0.15 (s, 18H), 1.31 (d, J=6.3 Hz,6H), 3.27 to 3.48 (complex m, 6H), 4.25 to 4,38 (complex m, 4H), 5.22 (ABq, J=13.6 Hz, $\Delta \upsilon_{AB}$= 50.5 Hz, 2H), 5.28 (ABq, J=13.7 Hz, $\Delta \upsilon_{AB}$ = 53.4 Hz, 2H), 7.23 (t, 7.6 Hz, 1H), 7.32 to 7.39 (m, 4H), 7.45 to 7.54 (m, 5H), 7.62 (t, J=7.5).Hz, 1H), 7.76 (t, J=7.7 Hz, 1H), 7.95 to 8.05 (m, 3H), 8.06 (d, J=8.6 Hz, 2H), 8.14 (d, J=8.2 Hz, 1H), 8.20 (s, 1H), 8.30 (s, 1H), 8.50 (d, J=8.3 Hz, 1H), 8.56 (d, J=7:7 Hz, 1H,) 11.12 (s, 1H), 11.54 (s, 1H).

IR ($CHCl_3$): 3400, 3040, 3010, 2960, 1775, 1725, 1665, 1610, 1520 cm^{-1}.

EXAMPLE 41

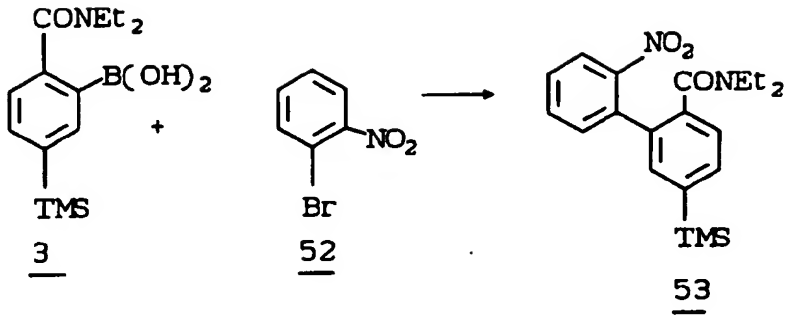


From an inseparable mixture of compounds 50 and 19 (80 mg, 0.13 mmol), using the general deprotection procedure described for compound 12, was provided 7.4 mg (13%) of carbapenem 51, a yellow solid, isolated via reverse phase prep-plate chromatography (6:1 H_2O/CH_3CN). The carbapenem 20 was also isolated in 32% yield (18.3 mg).

^{1}H-NMR for 51 [400 MHz, 2:1 D_20/CD_3CN]; δ 1.68 (d, J=6.3 Hz, 3H), 3.56 (½ ABX, J_{AB}=16.7 Hz, J_{AX}=9.7 Hz, 1H), 3.86 to 3.95 (complex m, 2H), 4.59 to 4.63 (m, 1H), 4.69 to 4.74 (m, 1H), 7.75 to 7.78 (m, 2H), 7.93 (t, J=7.9 Hz, 1H), 8.05 (d, J=8.1 Hz, 1H), 8.62 to 8.68 (m, 3H).

IR (KBr): 2970, 1750, 1660, 1650, 1610 cm-1. U.V. (MOPS Buffer): λ_o =322 nm, ε_o=13,300, λ_{ext1}=307 nm, ε_{ext1}=8,840; λ_{ext2}=330 nm, ε_{ext2}=7,970; λ_{ext3}=347 nm, ε_{ext3}=7,100.

EXAMPLE 42

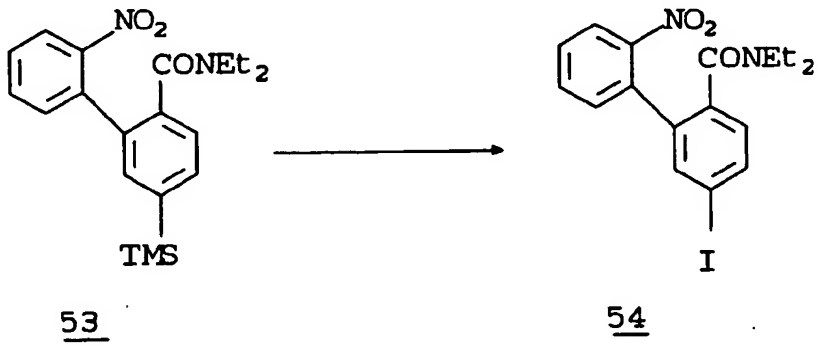


Following the Suzuki coupling procedure described for compound 5, boronic acid 3 (779.3 mg, 2.7 mmol) was coupled to aryl bromide 52 (590.5 mg, 2.9 mmol, 1.1 eq) providing 812.5 mg (82.5%) of biphenyl 53, a yellow foam.

^{1}H-NMR for 53 [400 MHz, $CDCl_3$, rotamers]; δ 0.24 (s, 9H), 0.80(t, J=7.1 Hz, 3H), 0.91(t, J=7.1Hz, 3H), 2.80 to 3.67 (broad, 4H), 7.30 to 7.33 (m, 2H), 7.46 (t, J=8.1 Hz, 1H), 7.52 to 7.58 (m, 3H), 7.90 (d, J=8.8 Hz, 1H).

IR ($CHCl_3$): 3000, 2980, 1610, 1580, 1525 cm^{-1}.

EXAMPLE 43

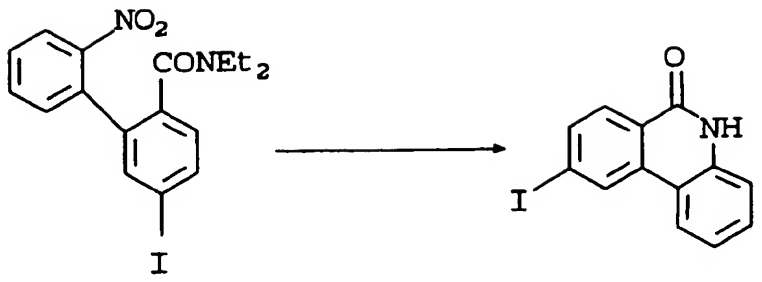


Iodine monochloride in dichloromethane (10.9 mL, 10.9 mmol, 5.0 eq) was added dropwise over 0.5 hour to a stirred solution of 53 (812.5 mg, 2.19 mmol) in dry dichloromethane (10.9 mL). The reaction mixture was then poured in ether (200mL) and washed with saturated sodium thiosulfate solution (2 x 25 mL), water, saturated bicarbonate solution (2 x 25 mL), water and brine. The etheral layer was then dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification using flash column chromatography (30% EtOAc/hex) afforded 887.7 mg (95.4%) of 54, a yellow foam.

^{1}H-NMR for 54 [400MHz, $CDCl_3$, rotamers]: δ 0.75 (t, J=7.0 Hz, 3H), 0.93 (t, J=7.0 Hz, 3H), 2.82 to 3.60 (broad, 4H), 7.07 (d, J=8.1 Hz, 1H), 7.46 to 7.51 (m, 2H), 7.56 to 7.60 (m, 2H), 7.73 (d, J=8.1 Hz, 1H), 7.97 (d, J=8.1 Hz, 1H).

IR ($CHCl_3$): 3000, 2980, 1620, 1580, 1525 cm^{-1}.

EXAMPLE 44

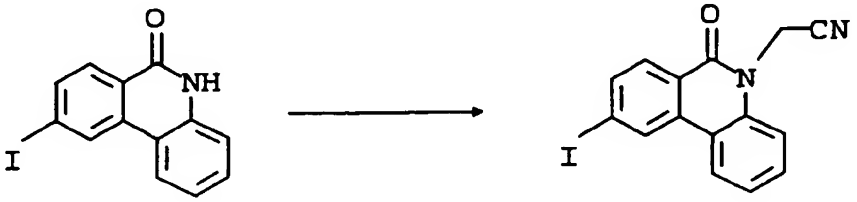


54 55

To a stirred solution of 54 (158.0 mg, 0.37 mmol) in 3:2:2 AcOH/EtOH/THF (7.0 mL) was added iron powder (103.8 mg, 1.86 mmol, 5.0 eq), and the reaction mixture was stirred at reflux until a white solid had separated (30 minutes). The reaction mixture was poured into ethyl acetate (200 mL) and washed with saturated sodium bicarbonate solution (1 x 25 mL), water, and brine. The organic layer was dried ($MgSO_4$) filtered and evaporated in vacuo. Chloroform (~10 mL) was added and the product was filtered to afford 119.0 mg (99.5%) of 55, a white solid.

^{1}H-NMR for 55 [400 MHz, D_6 DMSO]: δ 7.24 (t, J=7.7 Hz, 1H), 7.34 (d, J=8.1 Hz, 1H), 7.50 (t, J=7.6 Hz, 1H), 8.42 (d, J=8.1 Hz, 1 H), 8.89 (s, 1H). IR(KBr): 3010, 2990, 2870, 1665, 1600, 1585 cm^{-1}.

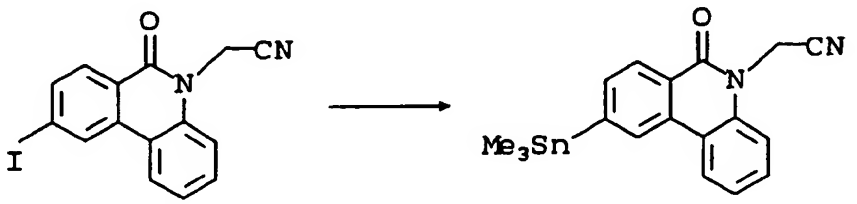
EXAMPLE 45



55 56

From 55 (143.0 mg, 0.44 mmol) and bromoacetonitrile (34.1 µL, 0.49 mmol, 1.1 eq), using the general alkylating procedure described for compound 24, was provided 124.1 mg (77.4%) of the N-cyanomethyl compound 56, a beige solid. 1H-NMR for 56 [400 MHZ, D_6 DMSO]: δ 5.50 (s, 2H), 7.42 (t, J=7.1 Hz, 1H), 7.66 to 7.72 (m, 2H), 8.01 (d, J=8.5 Hz, 1H), 8.06 (d, J=8.4 Hz, 1H), 8.59 (d, J=8.1 Hz, 1H), 8.94 (s, 1H).
IR(KBr): 3060, 2990, 2950, 1660, 1595 cm^{-1}.

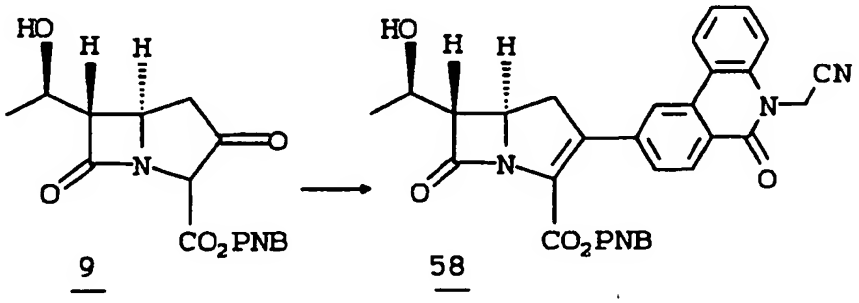
EXAMPLE 46



56 57

From 56 (120.0 mg, 0.33 mmol), using the general stannylation procedure described for compound 8, was provided 94.5 (70%) of stannane 57, a white solid.
^{1}H-NMR for 56 [400 MHz, $CDCl_3$]: δ 0.39 (s, 9H), 5.34 (s, 2H), 7.36 to 7.41 (m, 2H), 7.59 (t, J=7.8 Hz, 1H), 7.72 (d, J=7.7 Hz, 1H), 8.34 to 8.41 (m, 3H).
IR ($CHCl_3$): 3030, 3010, 2980, 1660, 1610, 1595, 1580 cm^{-1}.

EXAMPLE 47

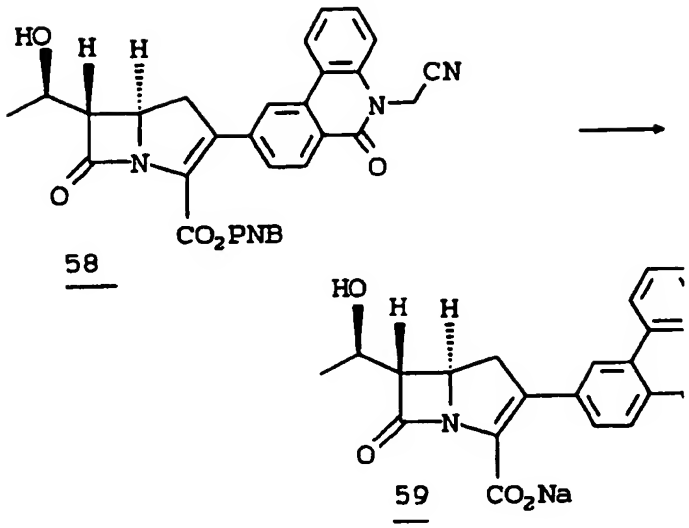


To a stirred solution of the bicyclic β-keto ester 9 (73.8 mg, 0.21 mmol) in dry THF (1.06 ml) at -78°C under N_2 was added diisopropylamine (32.7 µl, 0.23 mmol, 1.1 eq). The resultant yellow mixture was stirred for 10 minutes before trifluoromethanesulfonic anhydride (39.2 µl, 0.23 mmol, 1.1 eq) was added. After 20 minutes the reaction mixture was treated sequentially with anhydrous N-methylpyrrolidinone (1.06 mL), the $Pd_2(dba)_3{\cdot}CHCl_3$ catalyst (4.4 mg, 4.2×10^{-3} mmol, 2.0 mol%), the aryl stannane 57 (56.1 mg, 0.14 mmol, 0.66 eq), and zinc chloride (0.14 mL, 0.14 mmol, 0.66 eq). The low temperature bath was then removed and the reaction vessel was placed in a warm water bath to quickly reach ambient temperature. The resulting tea-color solution was stirred for 50 minutes at ambient temperature.

The reaction was then poured into ether (100 mL) and washed with water (3x) and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification using flash chromatography (70%, EtOAc/hex) provided 49.4 mg (61.9%) of the coupled product 58, a white solid.

^{1}H-NMR [400 MHz, D_6 DMSO]: δ 1.18 (d, J=6.2 Hz, 3H), 3.24 to 3.31 (m, 1H), 3.47 to 3.49 (m, 1H), 3.70 (½ABX, J_{AB}=18.4 Hz, J_{AX}=8.4 Hz, IH), 4.00 to 4.05 (m, 1H), 4.31 (t, J=8.3 Hz, 1H), 5.24 (ABq, J=14.5 Hz, $\Delta\upsilon_{AB}$=44.7 Hz, 2H), 5.50(s, 2H), 7.39 (d, J=8.4 Hz, 3H), 7.61 (d, J=8.1 Hz, 1H), 7.67 (d, J=3.9 Hz, 2H), 7.93 (d, J=8.6 Hz, 2H), 8.23 (d, J=8.4 Hz, 1H), 8.45 (d, J=7.8 Hz, 1H), 8.51 (s, 1H).
IR (KBr): 2920, 2855, 1775, 1720, 1660, 1605, 1518 cm^{-1}.
U.V. (CH_3CN): λ = 309 nm, ε = 6,317.

EXAMPLE 48



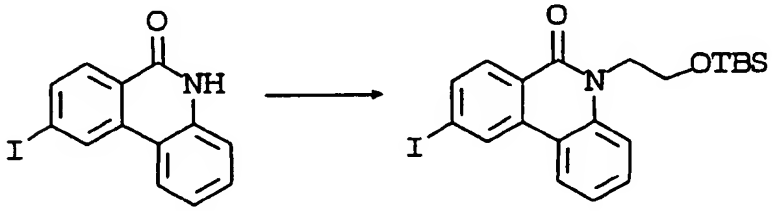
From 58 (55.4 mg, 9.8 x 10^{-2} mmol) and 1.0 M aqueous sodium bicarbonate solution (0.11 mL, 0.11 mmol, 1.2 eq), using the deprotection procedure described for compound 27, was provided 17.5 mg (39.5%) of carbapenem 59, a white solid.

^{1}H-NMR [400 MHz, 2:1 D_2O/CD_3CN]: δ 1.62 (d, J=6.5 Hz, 3H), 3.50 (½ABX, J_{AB}= 16.5 Hz, J_{AX}=9.8 Hz, 1H), 3.81 to 3.89 (complex m, 2H), 4.53 to 4.57 (m, 1H), 4.65 (t, J=9.1 Hz, 1H), 5.74 (s, 2H), 7.81 (t, J=7.6 Hz, 1H), 7.90 (d, J=8.1 Hz, 1H), 7.98 (d, J=8.4 Hz, 1H), 8.03 (t, J=7.5 Hz, 1H), 8.59 (d, J=8.4 Hz, 1H), 8.65 (s, 1H), 8.71 (d, J=8.1 Hz, 1H).

IR(KBr): 2970, 1750, 1645, 1610, 1585 cm^{-1}.

U.V. (MOPS Buffer): λ_o=328nm, ε_o=16,500; λ_{ext1}=331nm, ε_{ext1}=10,000; λ_{ext2}=345nm, ε_{ext2}=9,590.

EXAMPLE 49

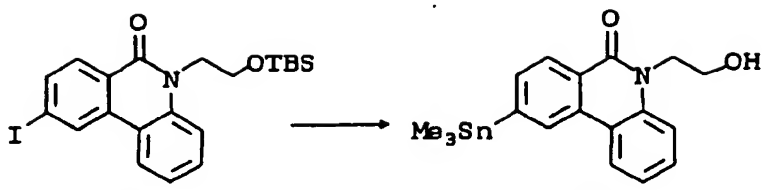


From 55 (200 mg, 0.62 mmol) and 2-bromo(t-butyldimethylsilyl)ethanol (0.23 mL, 1.24 mmol, 2.0 eq), using the general alkylating procedure described for compound 24, was provided 121.6 mg (40.7%) of 60, a white solid.

^{1}H NMR for 60 [400 MHz,$CDCl_3$]: δ -0.08 (s, 6H), 0.79 (s, 9H), 3.99 (t, J=6.2 Hz, 2H), 4.49(t, J=6.2 Hz, 2H), 7.27 (t, J=7.6 Hz, 1H), 7.50 (t, J=7.8 Hz, 1H), 7.64 (d, J=8.7 Hz, 1H), 7.85 (d, J=8.4 Hz, 1H), 8.14 (d, J=8.1 Hz, 1H), 8.19 (d, J=8.6 Hz, 1H), 8.59 (s, 1H).

IR($CHCl_3$): 3000, 2950, 2930, 2860, 2360, 1640, 1605, 1590, 1575.

EXAMPLE 50



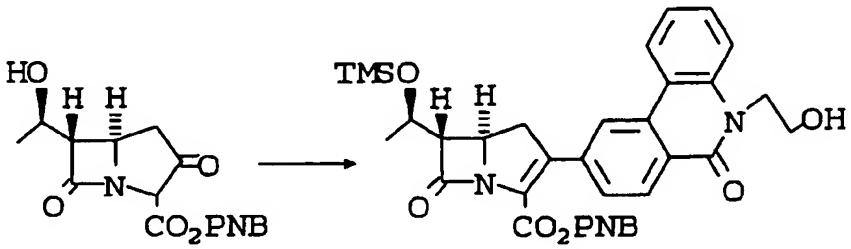
60 61

Iodide 60 (112.2 mg, 0.234 mmol) was stannylated following the general stannylation procedure described for compound 8. The crude TBS-protected stannane was then redissolved in dry THF (4.7 mL), and tetrabutylammonium fluoride (0.26 mL, 0.26 mmol, 1.1 eq) was added at 0°C. The reaction mixture was then stirred for 15 minutes at 0°C, poured into ethyl acetate, and washed with water (1x), saturated ammonium chloride solution (1x), water (2x), and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification using flash chromatography (45% EtOAc/hex) provided 76.8 mg (85%) of stannane 61, a white solid.

^{1}H-NMR for 61 [400 MHz,$CDCl_3$]: δ 0.39 (s, 9H), 2.98 (t, J=4.9 Hz, 1H), 4.10(t, J=5.3 Hz, 2H), 4.63 (t, J=5.5 Hz, 2H), 7.33 (t, J=6.9 Hz, 1H), 7.45 (d, J=7.6 Hz, 1H), 7.51 (d, J=7.8 Hz, 1H), 7.71 (d, J=7.7 Hz, 1H), 8.36 (d, J=8.2 Hz, 1H), 8.39 (s, 1H), 8.42 (d, J=7.9 Hz, 1H).

IR($CHCl_3$): 3560 to 3200, 3000, 2920, 1630, 1605, 1580 cm^{-1}.

EXAMPLE 51



9 62

To a stirred solution of the bicyclic β-keto ester 9 (158.3 mg, 0.45 mmol) in dry THF (2.3 mL) at -78°C under N_2 was added diisopropylamine (70.0 µL, 0.50 mmol, 1.1 eq). The resultant yellow mixture was stirred for 10 minutes before trifluoromethanesulfonic anhydride (84.1 µL, 0.50 mmol, 1.1 eq) was added. After 15 minutes triethylamine (69.7 µL, 0.50 mmol, 1.1 eq), followed by the trimethylsilyl trifluoromethanesulfonate (96.6 µL, 0.50 mmol, 1.1 eq), was added and the reaction mixture was stirred for 20 minutes.

The reaction mixture was then treated sequentially with anhydrous N-methylpyrrolidinone (2.3 mL), the $Pd_2(dba)3{\cdot}CHCl_3$ catalyst (9.4 mg, 9.1 x10^{-3} mmol, 2.0 mol%), the aryl stannane 61 (117.0 mg, 0.30 mmol, 0.66 eq), and zinc chloride (0.30 mL, 0.30 mmol, 0.66 eq). The low temperature bath was then removed and the reaction vessel was placed in a warm water bath to quickly reach ambient temperature. The solution was stirred for 30 minutes at ambient temperature.

The reaction was then poured into ether (150 mL) and washed with water (3x) and brine. The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo. Purification using flash chromatography (60% EtOAc/hex) provided 88.6 mg (45.5%) of the coupled product 62, a yellow oil.

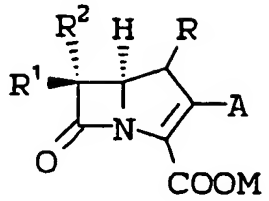
^{1}H-NMR for 62 [400 MHz, $CDCl_3$] δ 0.14 (s, 9H), 1.30 (d, J=6.2 Hz, 3H), 2.86 (t, J=4.8 Hz, 1H), 3.28 to 3.33 (complex m, 2H), 3.41 (½ABX, J_{AB}=18.5 Hz, J_{AX}=8.8 Hz, 1H), 4.08 (complex m, 2H), 4.24 to 4.28 (m, 1H), 4.34 (t, J=9.4 Hz, 1H), 4.61 (t, J=5.1 Hz, 2H), 5.20 (AB_q, J_{AB}=13.5 Hz, $\Delta\upsilon_{AB}$= 66.7 Hz, 2H), 7.22 to 7.28 (m, 3H), 7.43 to 7.47 (m, 2H), 7.50 (d, J=7.1 Hz, 1H), 7.89 (d, J=8.8 Hz, 2H), 8.03 (d, J=7.5 Hz, 1H), 8.16 (s, 1H), 7.44 (d, J=8.3 Hz, 1H).

IR($CHCl_3$): 3680 to 3200, 3010, 2960, 1780, 1730, 1640, 1610, 1585, 1525 cm^{-1}.

U.V. (CH_3CN): λ = 314 nm, ε = 16,210

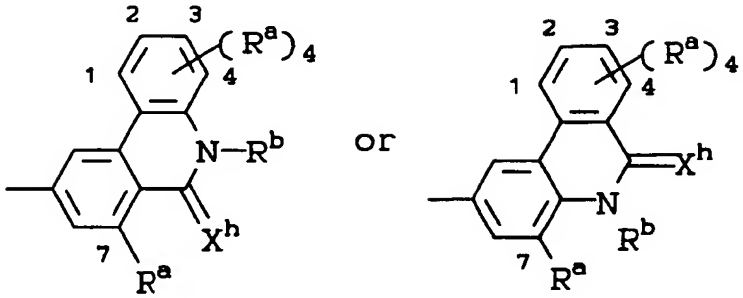
Claims

1. A compound of the formula:



where A is:

I



wherein:

R is H or CH_3;

X^h is O or S;

R^1 and R^2 are independently H, CH_3-, CH_3CH_2-, $(CH_3)_2CH$-, $HOCH_2$-, $CH_3CH(OH)$-, $(CH_3)_2C(OH)$-, $FCH_2CH(OH)$-, $F_2CHCH(OH)$-, $F_3CCH(OH)$-, $CH_3CH(F)$-, CH_3CF_2-, or $(CH_3)_2C(F)$-;

R^a are independently selected from the group consisting of hydrogen and the radicals set out below, provided that not more than four R^a and R^b radicals are other than hydrogen:

a) a trifluoromethyl group: $-CF_3$;

b) a halogen atom: -Br, -Cl, -F, or -I;

c) C_1-C_4 alkoxy radical: $-OC_{1-4}$ alkyl, wherein the alkyl is optionally mono-substituted by

R^q, where R^q is a member selected from the group consisting of -OH, $-OCH_3$, -CN, $-C(O)NH_2$, $-OC(O)NH_2$, CHO, $-OC(O)N(CH_3)_2$, $-SO_2NH_2$, $-SO_2N(CH_3)_2$, $-SOCH_3$, $-SO_2CH_3$, -F, $-CF_3$, $-COOM^a$ (where M^a is hydrogen, alkali metal, methyl or phenyl), tetrazolyl (where the point of attachment is the carbon atom of the tetrazole ring and one of the nitrogen atoms is mono-substituted by M^a as defined above) and $-SO_3M^b$ (where M^b is hydrogen or an alkali metal);

d) a hydroxy group: -OH;

e) a carbonyloxy radical: $-O(C=O)R^s$, where

R^s is C_{1-4} alkyl or phenyl, each of which is optionally mono-substituted by R^q as defined above;

f) a carbamoyloxy radical: $-O(C=O)N(R^y)R^z$ where

R^y and R^z are independently H, C_{1-4} alkyl (optionally mono-substituted by Rq as defined above), together a 3- to 5-membered alkylidene radical to form a ring (optionally substituted with Rq as defined above) or together a 2- to 4-membered alkylidene radical, interrupted by -O-, -S-, -S(O)- or -S(O)2-, to form a ring (where the ring is optionally mono-substituted with R^q as defined above);

g) a sulfur radical: $-S(O)_n-R^s$ where n = 0-2, and R^s is defined above;

h) a sulfamoyl group: $-SO_2N(R^y)R^z$ where R^y and R^z are as defined above;

i) azido: N_3

j) a formamido group: $-N(R^t)(C=O)H$, where

R^t is is H or C_{1-4} alkyl, and the alkyl thereof is optionally mono-substituted by R^q as defined above;

k) a (C_1-C_4 alkyl)carbonylamino radical: $-N(R^t)(C=O)C_{1-4}$ alkyl, where R^t is as defined above, and the alkyl group is also optionally mono-substituted by R^q as defined above;

l) a (C_1-C_4 alkoxy) carbonylamino radical: -N(R^t)(C=O)OC_{1-4} alkyl, where R^t is as defined above, and the alkyl group is also optionally mono-substituted by R^q as defined above;
m) a ureido group: -N(R^t)(C=O)N(R^y)R^z where R^t, R^y and R^z are as defined above;
n) a sulfonamido group: -N(R^t)SO_2R^s, where R^s and R^t are as defined above;
o) a cyano group: -CN;
p) a formyl or acetalized formyl radical: -(C=O)H or -$CH(OCH_3)_2$;
q) (C_1-C_4 alkyl)carbonyl radical wherein the carbonyl is acetalized: -$C(OCH_3)_2C_{1-4}$ alkyl, where the alkyl is optionally mono-substituted by Rq as defined above;
r) carbonyl radical: -(C=O)R^s, where R^s is as defined above;
s) a hydroximinomethyl radical in which the oxygen or carbon atom is optionally substituted by a C_1-C_4 alkyl group: -(C=NOR^z)R^y where R^y and R^z are as defined above, except they may not be joined together to form a ring;
t) a (C_1-C_4 alkoxy)carbonyl radical: -(C=O)OC_{1-4} alkyl, where the alkyl is optionally mono-substituted by R^q as defined above;
u) a carbamoyl radical: -(C=O)N(R^y)R^z where R^y and R^z are as defined above;
v) an N-hydroxycarbamoyl or N(C_1-C_4 alkoxy)carbamoyl radical in which the nitrogen atom may be additionally substituted by a C_1-C_4 alkyl group: -(C=O)-N(OR^y)R^z where R^y and R^z are as defined above, except they may not be joined together to form a ring;
w) a thiocarbamoyl group: -(C=S)N(R^y)(R^z) where R^y and R^z are as defined above;
x) carboxyl: -COOM^b, where M^b is as defined above;
y) thiocyanate: -SCN;
z) trifluoromethylthio: -SCF_3;
aa) tetrazolyl, where the point of attachment is the carbon atom of the tetrazole ring and one of the nitrogen atoms is mono-substituted by hydrogen, an alkali metal or a C_1-C_4 alkyl optionally substituted by Rq as defined above;
ab) an anionic function selected from the group consisting of: phosphono [P=O(OM^b)$_2$]; alkylphosphono {P=O(OM^b)-[O(C_1-C_4 alkyl)]}; alkylphosphinyl [P=O(OM^b)-(C_1-C_4alkyl)]; phosphoramido [P=O(OM^b)N(R^y)R^z and P=O(OM^b)NHR^x); sulfino (SO_2M^b); sulfo (SO_3M^b); acylsulfonamides selected from the structures CON$M^b$$SO_2R^x$, CON$M^b$$SO_2$N($R^y$)$R^z$, SO_2NM^bCON(R^y)R^z; and SO_2NM^bCN, where
R^x is phenyl or heteroaryl, where heteroaryl is a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, in which a carbon atom is the point of attachment, in which one of the carbon atoms has been replaced by a nitrogen atom, in which one additional carbon atom is optionally replaced by a heteroatom selected from O or S, and in which from 1 to 2 additional carbon atoms are optionally replaced by a nitrogen heteroatom, and where the phenyl and heteroaryl are optionally mono-substituted by R^q, as defined above; M^b is as defined above; and R^y and R^z are as defined above;
ac) C_5-C_7 cycloalkyl group in which one of the carbon atoms in the ring is replaced by a heteroatom selected from O, S, NH or N(C_1-C_4 alkyl) and in which one additional carbon atom may be replaced by NH or N(C_1-C_4 alkyl), and in which at least one carbon atom adjacent to each nitrogen heteroatom has both of its attached hydrogen atoms replaced by one oxygen thus forming a carbonyl moiety and there are one or two carbonyl moieties present in the ring;
ad) C_2-C_4 alkenyl radical, optionally monosubstituted by one of the substituents a) to ac) above and phenyl which is optionally substituted by Rq as defined above;
ae) C_2-C_4 alkynyl radical, optionally monosubstituted by one of the substituents a) to ac) above;
af) C_1-C_4 alkyl radical;
ag) C_1-C_4 alkyl mono-substituted by one of the substituents a) - ac) above;
ah) a 2-oxazolidinonyl moiety in which the point of attachment is the nitrogen atom of the oxazolidinone ring, the ring oxygen atom is optionally replaced by a heteroatom selected from -S- and NR^t (where R^t is as defined above) and one of the saturated carbon atoms of the oxazolidinone ring is optionally mono-substituted by one of the substituents a) to ag) above;

R^b is -H, -OH, -CF_3, -(C=O)R^s, -S(O)$_n$$R^s$ where n = 0-2, -SO_2N$R^y$$R^z$, -(C=O)O$C_{1-4}$alkyl, -(C=O)N($R^y$)$R^z$, -(C=O)N($OR^y$)$R^z$, -(C=S)N($R^y$)$R^z$, -$NH_2$, C_{1-4} alkoxy optionally mono-substituted with R^q, R^x as defined above, C_{1-4} alkyl optionally mono-substituted on an alpha carbon or higher by one of the substituents a)-ae) as defined for R^a;

M is selected from:
i) hydrogen;
ii) a pharmaceutically acceptable esterifying group or removable carboxyl protecting group; or
iii) an alkali metal or other pharmaceutically acceptable cation.

2. The compound of Claim 1 wherein R^1 is hydrogen and R^2 is (R)-$CH_3CH(OH)$- or (R)-$CH_3CH(F)$-.

3. A compound according to Claim 2 wherein R^a other than hydrogen is selected from the group consisting of:

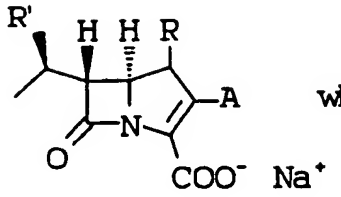
$-OCH_3$	$-OCH_2CO_2CH_3$
$-OCH_2CH_2OH$	$-CF_3$
$-F$	$-Cl$
$-Br$	$-I$
$-OH$	$-OCOCH_3$
$-OCONH_2$	$-SCH_3$
$-SOCH_3$	$-SO_2CH_3$
$-SCH_2CH_2OH$	$-SOCH_2CH_2OH$
$-SO_2NH_2$	$-SO_2N(CH_3)_2$
$-NHCHO$	$-NHCOCH_3$
$-NHCO_2CH_3$	$-NHSO_2CH_3$
$-CN$	$-CHO$
$-COCH_3$	$-COCH_2OH$
$-CH=NOH$	$-CH=NOCH_3$
$-CH=NOCH_2CO_2CH_3$	$-CH=NOCMe_2CONH_2$
$-CH=NOCMe_2CO_2Me$	$-CO_2CH_2CH_2OH$
$-CONH_2$	$-CONHCH_3$
$-CON(CH_3)_2$	$-CONHCH_2CN$
$-CONHCH_2CONH_2$	$-CONHCH_2CO_2CH_3$
$-CONHOH$	$-CONHOCH_3$
-tetrazolyl	$-CO_2CH_3$
$-SCF_3$	$-PO_2NH_2$
$-CONHSO_2Ph$	$-CONHSO_2NH_2$
$-SO_2CF_3$	$-SO_2NHCN$
$-SO_2NHCONH_2$	$-CH=CHCN$
$-CH=CHCONH_2$	$-CH=CHCO_2CH_3$
$-C\equiv C-CONH_2$	$-C\equiv C-CN$
$-CH_2OH$	$-CH_2N_3$
$-CH_2CO_2CH_3$	$-SO_2CH_2CH_2OH$
$-CH_2I$ and	$-SCH_2CONH_2$.

4. A compound according to Claim 2 wherein R^b other than hydrogen is selected from the group consisting of:

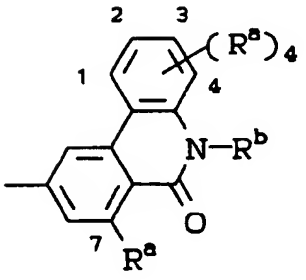
$-CH_2OCH_3$	$-CH_2OCH_2CO_2CH_3$
$-CH_2OCH_2CH_2OH$	$-CH_2CF_3$
$-CH_2CH_2F$	$-CH_2CH_2Cl$
$-CH_2CH_2Br$	$-CH_2CH_2I$
$-CH_2OH$	$-CH_2OCOCH_3$
$-CH_2OCONH_2$	$-CH_2SCH_3$
$-CH_2SOCH_3$	$-CH_2SO_2CH_3$
$-CH_2SCH_2CH_2OH$	$-CH_2SOCH_2CH_2OH$
$-CH_2SO_2NH_2$	$-SO_2N(CH_3)_2$
$-CH_2CH_2NHCHO$	$-CH_2CH_2NHCOCH_3$
$-CH_2CH_2NHCO_2CH_3$	$-CH_2CH_2NHSO_2CH_3$
$-CH_2CN$	$-CH_2CHO$
$-CH_2COCH_3$	$-CH_2COCH_2OH$
$-CH_2CH=NOH$	$-CH_2CH=NOCH_3$
$-CH_2CH=NOCH_2CO_2CH_3$	$-CH_2CH=NOCMe_2CONH_2$
$-CH_2CH=NOCMe_2CO_2Me$	$-CH_2CO_2CH_2CH_2OH$
$-CH_2CONH_2$	$-CH_2CONHCH_3$
$-CH_2CON(CH_3)_2$	$-CH_2CONHCH_2CN$
$-CH_2CONHCH_2CONH_2$	$-CH_2CONHCH_2CO_2CH_3$
$-CH_2CONHOH$	$-CH_2CONHOCH_3$
$-CH_2$tetrazolyl	$-CH_2CO_2CH_3$
$-CH_2SO_2CF_3$	$-CH_2PO_2NH_2$
$-CH_2CONHSO_2Ph$	$-CH_2CONHSO_2NH_2$
$-CH_2SO_2CF_3$	$-CH_2SO_2NHCN$
$-CH_2SO_2NHCONH_2$	$-CH_2CH=CHCN$
$-CH_2CH=CHCONH_2$	$-CH_2CH=CHCO_2CH_3$
$-CH_2C\equiv C-CONH_2$	$-CH_2C\equiv C-CN$
$-CH_2CH_2OH$	$-CH_2CH_2N_3$
$-CH_2CH_2CO_2CH_3$	$-CH_2SO_2CH_2CH_2OH$

$-CH_2SCH_2CONH_2$	$-OH$
$-OCH_3$	$-CF_3$
$-SO_2CH_3$	$-SO_2NH_2$ and
$-NH_2$.	

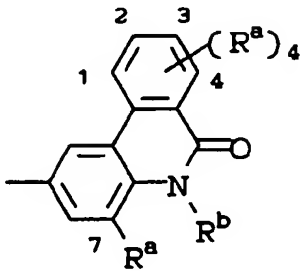
5. A compound of the formula:



where R' is F or OH, R is H or Me and A is:



or



wherein R^a and R^b are selected from the group consisting of

#	R^b	R^a	R^a position
1	-H	$-OCH_3$	7
2	-H	$-OCH_2CO_2CH_3$	7
3	-H	$-OCH_2CH_2OH$	4
4	-H	$-CF_3$	7
5	-H	-F	7,3,4
6	-H	-Cl	7,4
7	-H	-Br	7,4

#	R^b	R^a	R^a position
8	-H	-I	7
9	-H	-OH	7,4
10	-H	$-OCOCH_3$	7
11	-H	$-OCONH_2$	7
12	-H	$-SCH_3$	7
13	-H	$-SOCH_3$	7
14	-H	$-SO_2CH_3$	7
15	-H	$-SCH_2CH_2OH$	7
16	-H	$-SOCH_2CH_2OH$	4
17	-H	$-SCH_2CONH_2$	7
18	-H	$-SO_2NH_2$	7
19	-H	$-SO_2N(CH_3)_2$	3,4
20	-H	-NHCHO	7,4
21	-H	$-NHCOCH_3$	7
22	-H	$-NHCO_2CH_3$	7
23	-H	$-NHSO_2CH_3$	7
24	-H	-CN	7,3
25	-H	-CHO	7,4
26	-H	$-COCH_3$	7
27	-H	$-COCH_2OH$	4
28	-H	-CH=NOH	4
29	-H	$-CH=NOCH_3$	7
30	-H	$-CH=NOCH_2CO_2CH_3$	4
31	-H	$-CH=NOCMe_2CO_2CH_3$	3
32	-H	$-CH=NOCMe_2CONH_2$	7
33	-H	$-CO_2CH_2CH_2OH$	7
34	-H	$-CONH_2$	7,4
35	-H	$-CONHCH_3$	4
36	-H	$-CON(CH_3)_2$	7
37	-H	$-CONHCH_2CN$	7

#	R^b	R^a	R^a position
38	-H	$-CONHCH_2CONH_2$	7
39	-H	$-CONHCH_2CO_2CH_3$	7
40	-H	-CONHOH	7
41	-H	$-CONHOCH_3$	4
42	-H	-tetrazolyl	7
43	-H	$-CO_2CH_3$	4
44	-H	$-SCF_3$	7
45	-H	$-PO_2NH_2$	7
46	-H	$-CONHSO_2Ph$	7
47	-H	$-CONHSO_2NH_2$	7
48	-H	$-SO_2CF_3$	7
49	-H	$-SO_2NHCN$	7
50	-H	$-SO_2NHCONH_2$	7
51	-H	-CH=CHCN	7
52	-H	$-CH=CHCONH_2$	7
53	-H	$-CH=CHCO_2CH_3$	4
54	-H	$-C\equiv C-CONH_2$	7
55	-H	$-C\equiv C-CN$	4
56	-H	$-CH_2OH$	2
57	-H	$-CH_2N_3$	4
58	-H	$-CH_2CO_2CH_3$	4
59	-H	$-SO_2CH_2CH_2OH$	7
60	-H	$-CH_2I$	7
61	$-CH_2OCH_3$	$-OCH_3$	7
62	$-CH_2OCH_2CO_2CH_3$	$-OCH_2CO_2CH_3$	7
63	$-CH_2OCH_2CH_2OH$	$-OCH_2CH_2OH$	7
64	$-CH_2CF_3$	$-CF_3$	7
65	$-CH_2CH_2F$	-F	7
66	$-CH_2CH_2Cl$	-Cl	7
67	$-CH_2CH_2Br$	-Br	7

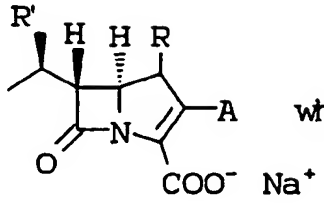
#	R^b	R^a	R^a position
68	$-CH_2CH_2I$	$-I$	7
69	$-CH_2OH$	$-OH$	7
70	$-CH_2OCOCH_3$	$-OCOCH_3$	7
71	$-CH_2OCONH_2$	$-OCONH_2$	7
72	$-CH_2SCH_3$	$-SCH_3$	7
73	$-CH_2SOCH_3$	$-SOCH_3$	7
74	$-CH_2SO_2CH_3$	$-SO_2CH_3$	7
75	$-CH_2SCH_2CH_2OH$	$-SCH_2CH_2OH$	7
76	$-CH_2SOCH_2CH_2OH$	$-SOCH_2CH_2OH$	7
77	$-CH_2SCH_2CONH_2$	$-SCH_2CONH_2$	7
78	$-CH_2SO_2NH_2$	$-SO_2NH_2$	7
79	$-SO_2N(CH_3)_2$	$-SO_2N(CH_3)_2$	7
80	$-CH_2NHCHO$	$-NHCHO$	7
81	$-CH_2NHCOCH_3$	$-NHCOCH_3$	7
82	$-CH_2NHCO_2CH_3$	$-NHCO_2CH_3$	7
83	$-CH_2NHSO_2CH_3$	$-NHSO_2CH_3$	7
84	$-CH_2CN$	$-CN$	1
85	$-CH_2CHO$	$-CHO$	7
86	$-CH_2COCH_3$	$-COCH_3$	7
87	$-CH_2COCH_2OH$	$-COCH_2OH$	7
88	$-CH_2CH=NOH$	$-CH=NOH$	7
89	$-CH_2CH=NOCH_3$	$-CH=NOCH_3$	7
90	$-CH_2CH=NOCH_2CO_2CH_3$	$-CH=NOCH_2CO_2CH_3$	7
91	$-CH_2CH=NOCMe_2CO_2Me$	$-CH=NOCMe_2CO_2CH_3$	7
92	$-CH_2CH=NOCMe_2CONH_2$	$-CH=NOCMe_2CONH_2$	7
93	$-CH_2CO_2CH_2CH_2OH$	$-CO_2CH_2CH_2OH$	7
94	$-CH_2CONH_2$	$-H$	*
95	$-CH_2CONHCH_3$	$-H$	*
96	$-CH_2CON(CH_3)_2$	$-H$	*
97	$-CH_2CONHCH_2CN$	$-H$	*

#	R^b	R^a	R^a position
98	$-CH_2CONHCH_2CONH_2$	-H	*
99	$-CH_2CONHCH_2CO_2CH_3$	-H	*
100	$-CH_2CONHOH$	-H	*
101	$-CH_2CONHOCH_3$	-H	*
102	$-CH_2$tetrazolyl	-H	*
103	$-CH_2CO_2CH_3$	-H	*
104	$-CH_2SCF_3$	-H	*
105	$-CH_2PO_2NH_2$	-H	*
106	$-CH_2CONHSO_2Ph$	-H	*
107	$-CH_2CONHSO_2NH_2$	-H	*
108	$-CH_2SO_2CF_3$	-H	*
109	$-CH_2SO_2NHCN$	-H	*
110	$-CH_2SO_2NHCONH_2$	-H	*
111	$-CH_2CH=CHCN$	-H	*
112	$-CH_2CH=CHCONH_2$	-H	*
113	$-CH_2CH=CHCO_2CH_3$	-H	*
114	$-CH_2C\equiv C-CONH_2$	-H	*
115	$-CH_2C\equiv C-CN$	-H	*
116	$-CH_2CH_2OH$	-H	*
117	$-CH_2CH_2N_3$	-H	*
118	$-CH_2CH_2CO_2CH_3$	-H	*
119	$-CH_2SO_2CH_2CH_2OH$	-H	*
120	$-CH_2CH_2I$	-H	*
121	-OH	-H	*
122	$-OCH_3$	-H	*
123	$-CF_3$	-H	*
124	$-SO_2CH_3$	-H	*
125	$-SO_2NH_2$	-H	*
126	$-NH_2$	-H	*
127	-H	$-CONH_2$	7

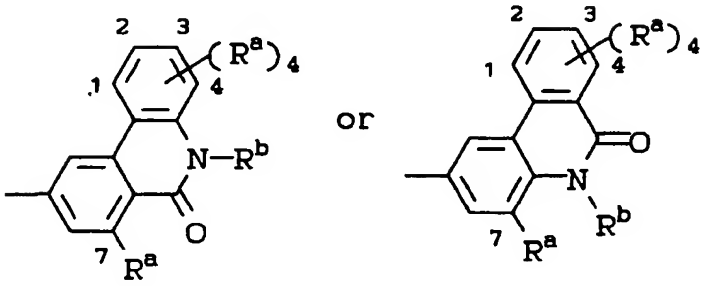
#	R^b	R^a	R^a position
128	-H	$-CONH_2$	4
129	-H	$-CONH_2$	3
130	-H	-CN	7
131	-H	-CN	4
132	-H	-CN	3
133	-H	-CHO	7
134	-H	-CHO	4
135	-H	-CHO	3
136	-H	$-CH_2OH$	7
137	-H	$-CH_2OH$	4
138	-H	$-CH_2OH$	3
139	$-CH_2CN$	$-CONH_2$	7
140	$-CH_2CN$	-CHO	7
141	$-CH_2CN$	$-CH_2OH$	7
142	$-CH_2CN$	-H	*
143	$-CH_2CN$	-CN	7
144	$-CH_2CN$	$-CONH_2$	3
145	$-CH_2CN$	-CN	3
146	$-CH_2CN$	$-CH_2OH$	3
147	$-CH_2CN$	-CHO	3
148	$-CH_2CN$	$-CONH_2$	4
149	$-CH_2CN$	-CN	4
150	$-CH_2CN$	$-CH_2OH$	4
151	$-CH_2CN$	-CHO	4
152	-H	$-SCH_3$	4
153	-H	$-S(O)CH_3$	4
154	-H	$-SO_2CH_3$	4
155	-H	$-SCH_3$	3
156	-H	$-S(O)CH_3$	3
157	-H	$-SO_2CH_3$	3

#	R^b	R^a	R^a position
158	-H	-Br	3
159	-H	-I	3
160	-H	-Br	4
161	-H	-I	4

6. A compound of the formula:



where R' is F or OH, R is H or Me and A is:

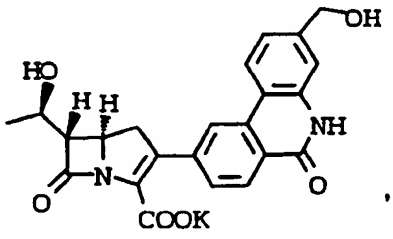


wherein R^a and R^b are selected from the group consisting of:

#	R^b	R^a	
1	-H	4-CHO	7-$CONH_2$
2	-H	4-CN	7-$CONH_2$
3	-H	4-CH_2OH	7-$CONH_2$
4	-H	3-CHO	7-$CONH_2$

#	R^b	R^a	
5	-H	3-CN	7-$CONH_2$
6	-H	3-CH_2OH	7-$CONH_2$
7	-H	3-CH_2OH	7-CN
8	-H	4-CH_2OH	7-CN
9	-H	4-CH_2OH	7-CN
10	-H	3-$CONH_2$	7-CN

7. A compound selected from a group consisting of:



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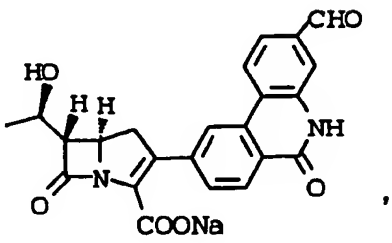

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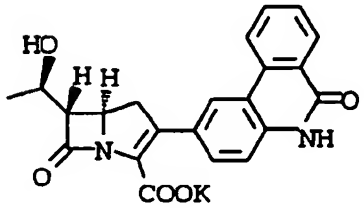

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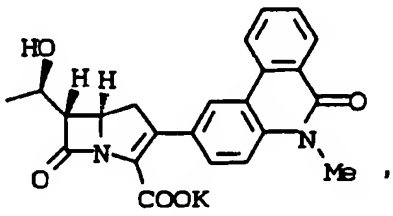

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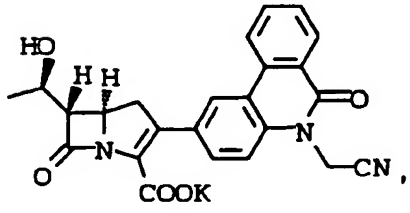

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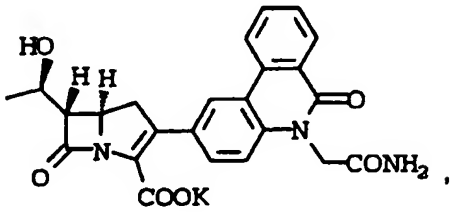

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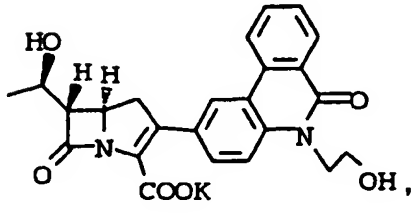

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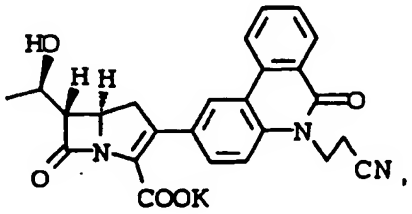

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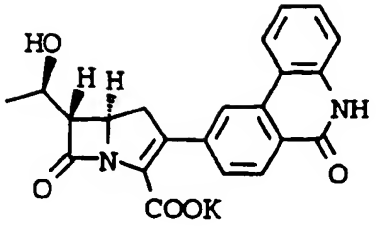
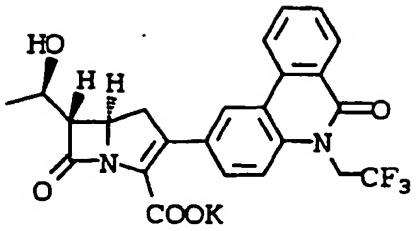
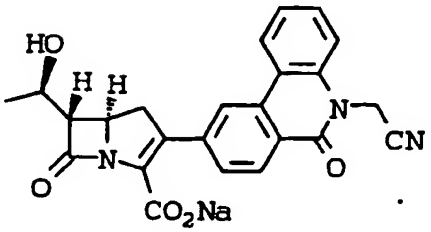
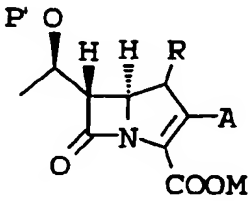




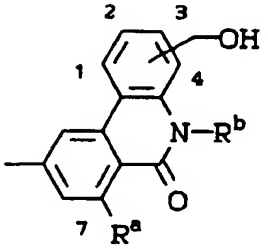
and



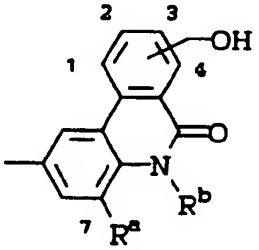
8. A compound of the formula:



where A is:



or



wherein

R is H or CH_3;

P′ is a removable protecting group for hydroxy;

M is a removable protecting group for carboxy;

R^a is selected from the group consisting of H, OP′, Cl, Br, I, SCH_3, CN, CHO, $SOCH_3$, SO_2CH_3, CO_2M , CH_2OP' or $CONH_2$;

R^b is H, OP′, CH_2SCH_3, CH_2CN, CH_2CHO, CH_2SOCH_3, $CH_2SO_2CH_3$, CH_2CO_2M , CH_2OP', CH_2CH_2OP' or CH_2CONH_2; and

with the proviso that the -CH_2-OH substituent is in the 3- or 4-position of the phenanthridone.

9. The compound of claim 8 wherein M is selected from the group consisting of benzhydryl, p-nitrobenzyl, 2-naphthylmethyl, allyl, 2-chloroallyl, benzyl, 2,2,2-trichloroethyl, trimethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, 2-(trimethylsilyl)ethyl, phenacyl, p-methoxybenzyl, acetonyl, o-nitrobenzyl 4-pyridylmethyl and t-butyl.

10. The compound of claim 8 wherein P′ is selected from the group consisting of t-butylmethoxyphenylsilyl, t-butoxydiphenylsilyl, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, o-nitrobenzyloxycarbonyl, p-nitroben-

zyloxycarbonyl, benzyloxycarbonyl, t-butyloxycarbonyl, 2,2,2-trichloroethyloxycarbonyl and allyloxycarbonyl.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 30 3376

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	US-A-5 004 739 (DININNO ET AL.) * claims *	1-10	C07D477/00 A61K31/40
D,A	EP-A-0 010 316 (MERCK & CO., INC.) * claims *	1-10	
P,A	US-A-5 025 007 (GREENLEE ET AL.) * claims *	1-10	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C07D
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	04 JUNE 1992	CHOULY J.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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E : earlier patent document, but published on, or after the filing date
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